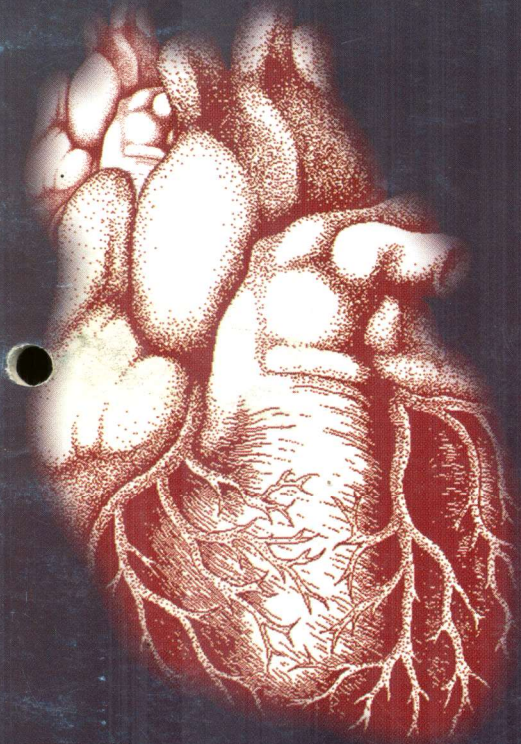


The ORION

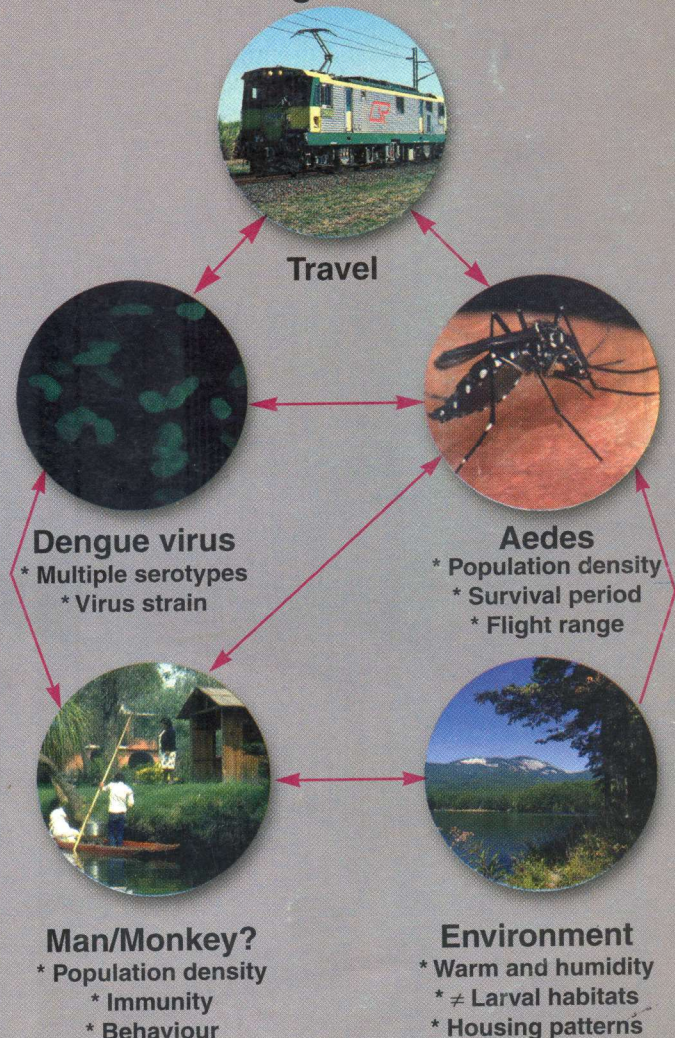
Medical Journal

Treatment of Heart Failure: Current Recommendation



Emergence of Haemorrhagic Dengue Fever in Bangladesh: Diagnosis, Management and Prospects for Control

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Editorial

We offer our deep gratitude and best compliments to our valued readers. Inspired by continuous support, appreciation, suggestion and comments of respected readers we are presenting 7th volume of our medical journal "The Orion".

We have the pleasure to announce that in addition to existing editorial board of the journal an Advisory Board and a Review Board have been formed. These two boards consist of highly qualified and reputed Medical Professionals and Scientists. Contributions of the honorable members of these boards will be very much helpful to enrich the journal and may give utmost satisfaction to the readers. A co-ordination meeting of honorable members of advisory board, review board and editorial board was held on August 12, 2000 at Pan Pacific Sonargaon hotel chaired by Professor M.A Quaderi, Vice- Chancellor, Bangabandhu Sheikh Mujib Medical University for further improvement and future planning of "The Orion".

Recently as a recognition of quality standard, our medical journal "The Orion" received International Standard Serial Number: ISSN 1606-9722. "The Orion" is the first medical journal among all publications of different pharmaceutical companies in the country to receive such registration number. We are very much grateful to the honorable writers of all previous issues as their articles and professional positions helped us to achieve such prestigious recognition.

We have been maintaining regularity in publishing medical journal from our maiden issue vol. 1, Sept 1998 with the help of valuable topics from dignified writers and sincere efforts of editorial board members. It is a matter of great satisfaction for us to have been able to publish this journal on various odds and to operate in close association with physicians.

Heart failure is one of the burning medical problems all over the world as a great portion of world population is suffering from this disease. Naturally this disease demands modern recommendation of treatment through research and trials and needs special attention from concerned section. In this issue modern recommendation of treatment of heart failure is focused through the article, "Treatment of heart failure: Current recommendation."

In the previous issue we highlighted the situation of Neonatal Health in Bangladesh and also alarmed the concerned authority about probability of present grave situation of Dengue and Dengue Haemorrhagic fever in Bangladesh as our country is geographically situated in Dengue affected area. Reports published in some dailies showed that few months ago vector *Aedes mosquito* was sporadically detected in some pockets of Dhaka city.

Considering present prevailing condition, in this issue we are again focussing on Dengue fever through the topic "Emergence of Dengue Haemorrhagic fever in Bangladesh - Diagnosis, Management and Prospects for Control" which will be helpful for the physicians to manage this stressful situation.

We are confident that our attempts in enlightening these problems will alert all concerned.

We hope by constant supervision, advice and support of the Advisory Board and the Review Board, our journal will achieve national and international acceptance and reputation.

Suggestions and recommendations from our readers are always most appreciable.



ATM Azizur Rahman
Chief Editor, "The Orion"
and

Manager, Medicinal Services Department.

MSD News

The members of Medical Services Department (MSD) of Orion Laboratories Ltd (OLL) spent a busy work schedule in the second quarter of the new Millennium. In addition to arranging seminars, launching Programme of new products and publication of medical journal, MSD of Orion Laboratories Ltd. & Orion Infusion Ltd. jointly with Department of Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), successfully completed an Efficacy Trial on Maprocin™ (Ciprofloxacin) and Nidazyl™ (Metronidazole) in both intravenous and oral forms under direct supervision of Prof. A. N. M. Atai Rabbi, FCPS, FICS, Chairman and Professor of Surgery, BSMMU. MSD conducted another Clinical Trial jointly with Department of Medicine, Dhaka Medical College Hospital (DMCH), and was successfully completed under the supervision of Professor Ferdous Ara J. Janan MBBS (Dha), MD (USA), FCPS (M), FRCP (Edin), FIBA (UK), Chairperson and Professor of Medicine, DMCH on Ortac™ (Ranitidine), Orixyl™ (Amoxicillin) and Nidazyl™ (Metronidazole) as a regimen of triple therapy in the eradication of *Helicobacter Pylori*. In this issue, we are presenting the abstract of the Efficacy Trial on Maprocin™ and Nidazyl™ and complete report of the Clinical Trial on triple therapy will be published later on in this journal.

SEMINARS

In Search of Ideal Antioxidant To Combat Cardiovascular Disease & Importance of Zinc For Health.

As part of continued programmes, MSD arranged seminars on above topics in the following venues:

Samorita Hospital Ltd. Dhaka, on May 08, 2000 chaired by Dr. A. B. M. Haroon, Managing Director, Samorita Hospital Ltd. MSD & BMA Feni jointly arranged a seminar at Doctor's Recreation Club, Feni chaired by Dr. Dawoodul Islam, President, BMA, Feni. Dr. Mainuddin Ahmed Chowdhury, Civil Surgeon, Feni was chief Guest of the seminar. Jamalpur General Hospital on June 07, 2000 chaired by Dr. Hamidullah Feroz, Civil Surgeon, Jamalpur.

Role of Zinc in Child Health

On the occasion of launching of **Pep** (Zinc Sulphate Syrup), MSD arranged a number of seminars on the above topic in following venues:

Department of Paediatrics, Dhaka National Medical College Hospital (DNMCH) on July 18, 2000 chaired by Dr. Md. Saifur Rahman, Associate Professor and Head of the Deptt. of Paediatrics, DNMCH. Bangladesh Institute of Child Health (BICH) & Dhaka Shishu Hospital on July 23, 2000 chaired by Prof. Manzoor Hussain, Director and Professor, Dhaka Shishu Hospital. National Professor M. R. Khan was Chief Guest of the seminar. Prof. Salim Shakur, Professor & Senior Consultant, BICH & Dhaka Shishu Hospital was the Key Note Speaker. Other speakers on the topic were: Prof. M. A. K. Azad Chowdhury, Professor & Senior Consultant, BICH & Dhaka Shishu Hospital, Prof. M. A. Kashem Sarkar, Professor & Senior Consultant, BICH & Dhaka Shishu Hospital and Dr. S. K. Roy, Scientist, Clinical Sciences Division, ICDDR,B. Institute of Child and Maternal Health (ICMH), Matuail, Dhaka, chaired by Prof. M Q-K Talukdar, Director, ICMH, Matuail, Dhaka. Department of Paediatrics, Women Medical College Hospital (WMCH) & Shahid Mansur Ali Medical College Hospital (SMAMCH) on July 31, 2000 chaired by Dr. Chowdhury Md. Haider Ali, Assistant Professor, Deptt. of Paediatrics, WMCH, Uttara, Dhaka. Prof. Mahmudul Karim, Professor & Head of the Deptt. of Paediatrics, SMAMCH and Dr. Md. Ishtiaque Hossain, Associate



Picture of the Seminar at BICH. Key Note Speaker Prof. Selim Shakur addressing the audience. From left hand side. (Sitting): Prof. Khairul Amin, National Professor M. R. Khan, Prof. Manzoor Hossain & Dr. ATM Azizur Rahman.

Professor & Head of the Deptt. of Paediatrics, were Guest of Honour and Chief Guest of the seminar. Department of Paediatrics, Dhaka Medical College Hospital (DMCH), Dhaka, on August 14, 2000 chaired by Prof. Nazmun Nahar, Professor and Head of the Deptt. of Paediatrics, DMCH and Brig. Badrul Munir, Director, DMCH was the

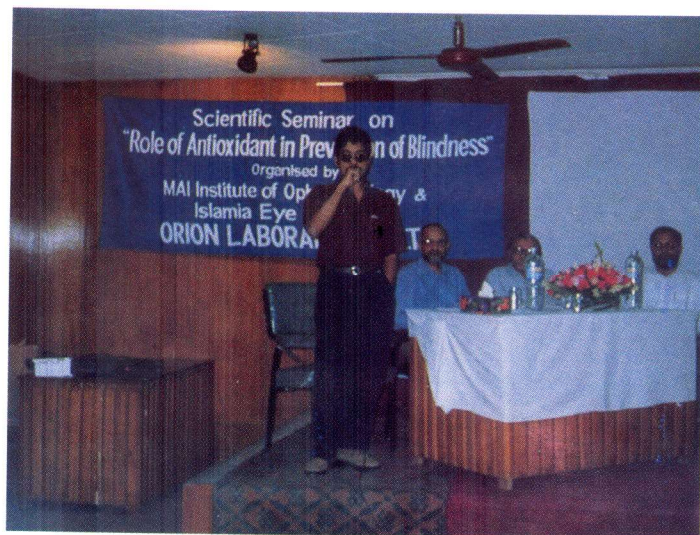


Picture of the Seminar at DMCH From left hand side: Assoc. Prof. Hosne Ara Begum Prof. Nazmun Nahar & Brig. Badrul Munir

chief guest. Department of Paediatrics, Bangladesh Medical College Hospital (BMCH), Dhaka, on August 19, 2000 chaired by Dr. Mohammad Nurul Huq, Associate Professor & Head of the Deptt. of Paediatrics, BMCH, Dhaka.

Role of Antioxidant in Prevention of Blindness

MSD further arranged a seminar on August 05, 2000 on most important topic 'Role of Antioxidant in Prevention of Blindness' at MAI Institute of Ophthalmology and Islamia Eye Hospital, Dhaka chaired by Major General (Dr.) Mukhlesur Rahman, Director, Islamia Eye Hospital (IEH), and Professor Mustafizur Rahman, Director, MAI Institute of Ophthalmology & Chief Consultant, Islamia Eye Hospital, Dhaka was the Key-note Speaker. Among others Dr. Niaz Rahman,



Picture of the Seminar at IEH. Asstt. Prof. Nazmul Haque Robi (Rapporteur) addressing the audience. From lefthand side (Sitting): Major General (Dr.) Mukhlesur Rahman, Key note speaker Professor Mustafizur Rahman & Dr. ATM Azizur Rahman.

Consultant, MAI Institute of Ophthalmology & IEH, Dr. Md. Nazmul Haque Robi, Course Coordinator (Asst. Prof.) & Consultant, MAI Institute of Ophthalmology & IEH and Dr. ATM Azizur Rahman, Manager, MSD, OLL delivered valuable speech.

FIRST CO-ORDINATION MEETING OF THE ADVISORY & THE REVIEW BOARD OF "The ORION" Medical Journal

The First Co-ordination Meeting of "The ORION" was held on August 12, 2000 at Pan Pacific Sonargaon Hotel, Dhaka. The meeting was chaired by Professor M. A. Quaderi, Vice Chancellor, Bangabandhu Sheikh Mujib Medical University (BSMMU) and inaugurated by Prof. (Maj. Gen.) Anis Waiz, Principal and Professor of Medicine, Bangladesh Medical College. Mr. Ebadul Karim, Director Marketing of Orion Laboratories Ltd. welcomed the participants. The following eminent Medical Professionals of the Advisory and the Review board were present and gave their valuable suggestions regarding improvement of "The ORION"-

E.N.T. specialist Prof. M. A. Majed, Gynaecologist & Obstetrician Prof. T. A. Chowdhury, Eye Specialist Prof. Mustafizur Rahman, Surgeon Prof. ANM Atai Rabbi, Neurologist Prof. Anisul Haque, Cardiologist Prof. Hasina Banu, Scientists from ICDDR,B Dr. G. H. Robbani & Dr. Mahbubur Rahman, Paediatrician Prof. M. A. K. Azad Chowdhury, Nutrition Expert Prof. Khursheed Jahan, Neurologist Prof. Deen Mohammad and Cardiologist Prof. Mamtaz Hossain.

In his speech, Prof. Maj. Gen. Anis Waiz advised the Editorial board to make the journal easily understandable and acceptable to the general practitioners. While Prof. T. A. Chowdhury comment "The Orion" as an exceptional one and advised to maintain the standard for Continued Medical Education (CME). Prof. Hasina Banu suggested to keep an option for Bengali topics in the journal. Among others, Prof. Anisul Haque, Scientist Dr. G. H. Robbani & Dr. Mahbubur Rahman of ICDDR,B, and the Chief Editor of "The ORION", Dr. ATM Azizur Rahman delivered constructive speeches.

In concluding speech Prof. M. A. Quaderi advised to publish "The ORION" in three forums, namely 1) Specialist's Forum, 2) General Practitioner's Forum & 3) Nutrition Forum. He requested the honourable members to write articles for this journal and thus fulfill their commitment to the society. Further more, he congratulated MSD of Orion Laboratories Ltd. for being rewarded with the International Standard Serial Number (ISSN) and assured all sort of co-operations from his side.



Picture of the Co-ordination Meeting of the Advisory & The Review Board at Sonargaon Hotel. From left hand side: Dr. ATM Azizur Rahman, Prof. T. A. Chowdhury, Prof. Maj. Gen. Anis Waiz, Prof. M. A. Quaderi, Mr. Ebadul Karim & Dr. Md. Mahmud Hasan.

The meeting also condoled the sad demise of Prof. Sayeda Feroza Begum, renowned gynaecologist of the country and Ex. President, BMA and prayer was offered for the departed soul.

LAUNCHING OF NEW PRODUCTS

Pep (Zinc Sulphate Syrup)

Recently Orion Laboratories Ltd. launched Pep (Zinc Sulphate Syrup) the long desired product of Paediatricians, for the first time in Bangladesh. Because Pep is essential for the treatment of Zinc deficiency & as a routine supplementation for the growing children. The palatable lemon flavoured 100 ml syrup shows a tremendous result in children with serious health hazards like respiratory tract infections, severe growth retardation, diarrhoea, impaired immunological response etc. On the occasion of launching of Pep, MSD arranged a number of seminars throughout the country.

CCB (Amlodipine INN 5mg & 10 mg)

For effective control of Hypertension and Angina, Orion Laboratories Ltd. has introduced CCB (Amlodipine INN 5mg & 10 mg). Efficacy and safety of CCB with once daily dosage regimen makes the drug an excellent choice for hypertensive and angina patients.

ESP (Zinc sulphate 61.8 & Folic acid 500 mcg)

For safe use during first trimester of pregnancy, Orion has recently introduced a new product ESP (Zinc sulphate 61.8 & Folic acid 500 mcg). It is an essential product which is also safe in pregnancy. A preferred combination of Zinc & Folic acid for pregnant women from the beginning of pregnancy makes it an ideal drug of choice.

EFFICACY TRIAL ENDING CEREMONY AT BSMMU

MSD of Orion Laboratories Ltd. & Orion Infusion Ltd. jointly with Department of Surgery, BSMMU, arranged a seminar on "Management of Post-operative Infection" on June 29, 2000 at the Department of Surgery, BSMMU on the occasion of Efficacy Trial Ending Ceremony. The seminar was chaired by Professor A. N. M. Atai Rabbi, FCPS, FICS, Chairman and Professor of Surgery, BSMMU. Dr. Saif-ud-Dowla Khan, Resident-in-charge, Surgery unit I-A, BSMMU, presented the paper on the Efficacy Study. Later Certificate on Efficacy Study of Maprocin™ and Nidazyl™ was awarded by the Chairperson. The excellent result of the Efficacy Trial scientifically prove the quality and merits of the brand as an appropriate antibiotic regimen. The abstract of the study and Certificate awarded by Department of Surgery, BSMMU, has been shown in the abstract at page 25.

Treatment of Heart Failure : Current Recommendation

Anis Waiz

The impaired left ventricular emptying that characterizes heart failure may result from a variety of cardiac diseases, including myocardial ischaemia or infarction (that alters regional function), cardiomyopathies (that alter global function), and pressure or overload states (that lead to hypertrophy and dilatation of the chamber). This functional abnormality of the left ventricle is an important contributor to symptoms of heart failure and plays a critical role in the sodium retention that leads to congestion in the pulmonary circulation and oedema in the systemic circulation. Consequently, efforts to enhance the contractile force of the left ventricle have characterized strategies for the management of heart failure for the past generation.

The syndrome of heart failure results from various cardiovascular disorders and is characterized by systolic and/ or diastolic dysfunction. Although central haemodynamic abnormalities are by definition the initiating pathological event in this syndrome, it has been shown that the degree of left ventricular dysfunction does not correlate with exercise tolerance or symptoms. This can be explained, in part, by the complex interplay between central haemodynamic, pulmonary factors and peripheral circulation, as well as by neuroendocrine adaptation. The most frequent symptom of heart failure is exercise intolerance associated with dyspnoea and fatigue upon exertion. Heart failure is associated with high morbidity and mortality¹. Annual mortality rates of 20-40% have been reported for systolic dysfunction and 10-20% for diastolic dysfunction, depending on the severity of the disease.

Heart failure is characterized by a number of neurohormonal abnormalities. These include: the sympathetic nervous system, as indicated by an elevated plasma norepinephrine level², the renin-angiotensin system, as identified by an increase in

plasma renin activity², increased plasma level of aldosterone; increased activity of the endothelin system with increased plasma levels of big endothelium as well as ET-1³, increased activity of cytokines as shown by an increase in TNF α ⁴, increased arginine vasopressin levels⁵ and probably other systems not fully elucidated. Although not all of these systems have fully studied in terms of their role in remodeling and the efficacy of their inhibition, growing evidence supports a potential direct contribution of norepinephrine, angiotensin II, aldosterone, endothelin and TNF α in the progressive structural process.

The association between elevation of circulating effector hormones of the renin-angiotensin-aldosterone system (RAAS) and the progression of congestive heart failure is now irrefutable. In keeping with this, angiotensin-converting enzyme (ACE) inhibitors have been shown to be effective in reducing the incidence of hospitalization and the rate of mortality in patients with systolic left ventricular dysfunction^{6,7}.

PRACTICAL ASPECTS OF TREATMENT OF SYSTOLIC AND DIASTOLIC DYSFUNCTION

In general, heart failure therapy implies treatment of systolic dysfunction. However, it is expected that diastolic dysfunction (typically a heart disease of the elderly hypertensive) will receive greater attention in the future. Nonetheless, clinicians must clearly understand how the therapy for systolic and diastolic dysfunction in heart failure differs. The various approaches to heart failure management are outlined:

In patients with dyspnoea and pulmonary congestion, diuretics remain the initial agents⁸. Once these congestive symptoms have ameliorated, an ACE-inhibitor or an α -II blocker should be added to improve cardiac function by reducing afterload and blocking neurohormonal stimulation. Spironolactone should be added not for its diuretic but for its beneficial effect on cardiac remodelling and reducing the collagen content of

Prof. (Maj. Gen.) Anis Waiz

MBBS, FCPS, FRCP(I), FRCP (Ed), FACP

Principal & Professor of Medicine,

Bangladesh Medical College.

the heart⁽⁹⁾, which may improve diastolic dysfunction. The RALES (Randomized Aldactone Evaluation Study) trial has recently demonstrated the short and long term benefit of spironolactone in patients with severe heart failure. Patients treated with spironolactone and standard therapy, which included ACE-inhibitors and diuretics showed a 30% reduction of mortality over a 2-year period¹⁰. In the RALES trial¹⁰, selection criteria required patients to have a history of NYHA class IV heart failure and a left ventricular ejection fraction $\leq 35\%$ within the 6 months prior to enrollment. At the time of randomization the patients were in either class III or IV heart failure, while maintained on standard therapy (an ACE-inhibitor, if tolerated, and a loop diuretics with or without digoxin). The dose of spironolactone was chosen on the basis of a prior carefully performed parallel dose-finding study in which it was shown that 25mg of spironolactone was pharmacologically effective and didn't result in significant hyperkalaemia¹¹.

The investigators were allowed to reduce the dose of study medication to 25mg every other day if they saw any tendency toward hyperkalaemia. If, however, after eight weeks there was no evidence of hyperkalaemia but there was evidence of progressive heart failure, the doses of study medication could be increased to 50mg daily. The patients in this trial were to have been followed for three years with the end-point of total all-cause mortality. However, the trial was prematurely stopped at the end of a two year mean follow-up because the data safety Monitoring Committee found that there was a significant mortality benefit in patients who were randomized to spironolactone. Beta-blockers have shown to improved symptomatology and reduce mortality. In severely symptomatic patients; however, "start low, go slow" should be considered.

The next step is to add digitalis, which does not reduce mortality but improves symptoms and reduces the rate of hospitalization. It should be noted that digitalis is particularly indicated in patients with systolic dysfunction who remain symptomatic. Digitalis is not indicated in patients with diastolic dysfunction, except for rate control in the presence of atrial fibrillation.

The second cornerstone in heart failure therapy is the use of beta-blocker¹². These agents have profound and important effects on survival of patients with systolic dysfunction. However, it is

unclear whether patients with diastolic dysfunction experience a beneficial effect. In patients with coronary artery disease beta-blockers improve function by reducing heart rate with a resulting prolongation of diastolic interval and, thus an improvement of diastolic filling. Between 1980 and 1997, 24 randomized controlled trials of beta-blockers in heart failure were reported^{13,14}. These trials included a total of 3141 patients with ischaemic or non - ischaemic causes of heart failure; more than 80% were on standard ACE-inhibitor treatment. A meta analysis showed a 31% reduction in mortality with beta-blocker and mean annual mortality being reduced from 9.7% to 7.5%¹⁴.

MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) is the largest trial, which included 3991 patients with heart failure in NYHA functional class II-IV and with left-ventricular ejection fraction of under 40%, on standard therapy. Treatment with long-acting metoprolol conferred a 34% reduction in mortality, annual mortality being reduced from 11.0% to 7.2%.

ACE-inhibitors in heart failure improve symptoms, haemodynamics, ventricular remodelling and survival. The survival benefit from an overview of controlled trial data (32 trials in 7105 patients) ranges from 12% to 33%¹⁵, and it is due primarily to a reduction in deaths from worsening heart failure, but there is no clear evidence of a reduction in sudden death. The effect of Beta-blockade seems additive to that of ACE inhibition. In both CIBIS-II (Cardiac Insufficiency Bisoprolol Study) and MERIT-HF, sudden deaths were significantly reduced. Deaths from progressive heart failure were significantly reduced in MERIT-HF and showed a trend to reduction in CIBIS-II. In MERIT-HF, sudden death was more common with less severe heart failure. Overall, this treatment effect strongly suggest an effective anti-arrhythmic action of beta-blockade, which may itself be favourably influenced by several subsidiary mechanisms, such as alterations in cardiac electrophysiology, autonomic activity, energy balance and ventricular remodelling.

Patients with severe class IV heart failure have generally been excluded from recent trials and experience in such patients is limited. The designation of patients in recent trials as "stable class IV" implies unjustified precision.

Which beta-blocker is best? The US carvedilol trial¹⁶ suggested the possibility that carvedilol may provide greater benefit than other selective agents, perhaps because of its vasodilator and other ancillary actions. The results of CIBIS-II¹⁷ and MERIT-HF, however, now indicate that the predominant effect is most probably a class effect of beta-blockers. Thus for the present, treatment with either carvedilol, bisoprolol or metoprolol can be recommended.

Patients with clinically stable heart failure and left ventricular systolic dysfunction established on standard treatment should be considered for beta-blocker therapy. Contraindications should be carefully observed. Treatment aims should be considered realistically, the principal benefits being a reduction in hospital stay and longer survival rather than symptom relief. Carvedilol, bisoprolol or metoprolol in the formulation as used in the trials can be recommended, starting with low dose and increasing gradually over weeks or months. Treatment can, with care, be established on an outpatient basis with monitoring for predictable side effects. The benefit of beta-blocker treatment for heart failure is now certain and substantial and should be incorporated into modern practice guidelines¹⁸.

The newer generation of calcium antagonists having minimal negative inotropic effect is not indicated for treating patients with symptomatic heart failure. However, it is well known that calcium antagonists have a positive lusitropic effect, which enhances myocardial relaxation and increases filling. Thus, these drugs may be helpful to improve diastolic filling in patients with diastolic dysfunction. In presence of severe reduction of left ventricular function, or when atrial fibrillation ensues, anticoagulation is necessary to prevent thromboembolic complications. This benefit of anticoagulation is useful for both systolic and diastolic dysfunction.

When all medical therapy fails in patients with end stage heart failure, cardiac transplantation becomes an option, which is not unusual for patients with systolic dysfunction but rarely occurs in cases of diastolic dysfunction. Newer drugs on the horizon for the treatment of heart failure include the neuropeptidase inhibitors, which may be an addition to therapy. These agents, such as omapatrilat, block the RAAS system and at the same time decrease degradation of atrial

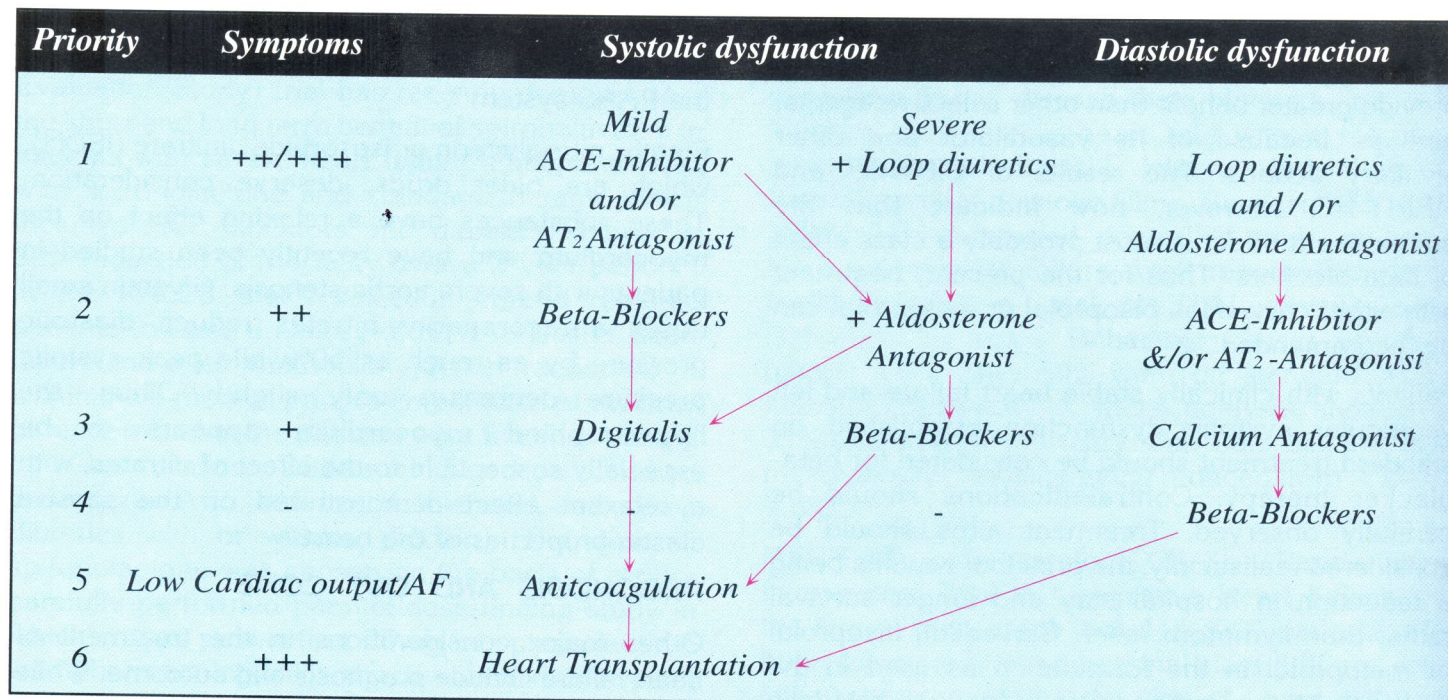
natriuretic peptides. Thus, these compounds have diuretic effects in addition to the effect of blocking the RAAS system¹⁹.

Finally, nitroglycerin or isosorbide dinitrate (ISDN), which are older drugs, deserve consideration. These substances have a relaxing effect on the myocardium and have recently been studied in patients with severe aortic stenosis. Given in small doses intracoronarily nitrates reduce diastolic pressure by as much as 50% while peak systolic pressure decreases only slightly²⁰. Thus, the hypertrophied myocardium appears to be especially susceptible to the effect of nitrates, with a relaxant effect demonstrated on the passive elastic properties of the heart.

PROGNOSIS AND OUTCOME

Other major considerations in the treatment of heart failure include prognosis and outcome. While haemodynamics and neurohormonal factors play key roles in determining prognosis, genetic phenotype has been found to be particularly important in determining outcome. In the future it may be possible to identify patients who are at risk for premature death because of their specific phenotype. An example of this concept is beta-receptor polymorphism, in which the difference of one amino acid in the beta-adrenoceptor has been found to correlate with a favourable or unfavourable prognosis over a three year period²¹. Thus, detection of genetic polymorphism will be an important tool in the future to identify patients who are at high risk for a premature death from heart failure.

Genetic phenotype may also prove to be important in determining therapy. For example, in a recent study²², AT₁ receptor genotype was determined in a group of patients who received either ACE inhibitor therapy or calcium antagonist therapy. While ACE inhibitor therapy decreased cardiac wall thickness in patients with phenotypes AA, AC and CC, calcium antagonist therapy reduced myocardial mass only in patients with AA phenotype. Thus, it may become necessary to identify the genetic phenotype of a patient before an appropriate antihypertensive or heart failure drug can be initiated. Such management would be expected to help reduce costs as well as to increase the efficacy of drug therapy.



Adapted from Hess OM. *Eur Heart J*. 2000; 2 (suppl A): P - A 15.

CONCLUSION

Morbidity and mortality can be reduced considerably in NYHA Class III and Class IV heart failure patients by the combine use of ACE inhibitors and beta-blockers. Now aldosterone antagonists have emerged as important drugs for further improving survival and quality of life in heart failure patients. Mortality rates of 10-15% per annum have become realistic in patients with advanced heart failure, and are approaching the mortality rates observed in transplanted patients.

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Emergence of Dengue Haemorrhagic Fever in Bangladesh: Diagnosis, Management and Prospects for Control.

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Introduction

Dengue is an acute febrile mosquito-borne disease caused by four antigenically related serotypes of dengue viruses in tropical and subtropical areas of the world putting more than 3 billion people at risk of infection. An estimated 50 - 100 million of dengue cases occur yearly resulting in 500,000 hospitalisation and 25,000 deaths. The patterns of dengue viral diseases vary and include commonly mild undifferentiated fever, classical dengue fever (DF) and life-threatening dengue haemorrhagic fever (DHF) frequently leading to hypovolemic shock i. e. dengue shock syndrome (DSS) with a significant case-fatality rate up to 44% if early diagnosis followed by careful and timely proper case-management are not performed. Classical dengue fever is characterised by fever, pain symptoms (headache, muscle and joints pain, retroorbital pain), rash and gastrointestinal symptoms (vomiting, nausea, loss of appetite and diarrhoea). The febrile phase is usually followed by a short afebrile phase (defervescence phase) and a relatively long convalescence phase. Between 1635 and 1886, dengue infection was primarily clinically expressed as relatively mild dengue fever without a significant morbidity and mortality in the world. However, dengue cases with haemorrhage, shock and death were reported for the first time in 1887 in Queensland, Australia. The severe nature of DHF was not well recognized till 1953 when a large epidemic of DHF (Philippines fever) occurred in Manila, Philippines. The epidemic remained localized in Southeast Asia till the 1970s involving Thailand, Myanmar and other neighbouring countries. In the 1980s and 1990s the epidemic DHF spread west into India, Pakistan, Sri Lanka, Maldives and probably Bangladesh and east into China. Nearly 30 years after its appearance in Asia, the first epidemic DHF emerged in the Americas in Cuba in 1981 and by now many American countries are affected with DHF. Currently, DHF is an important cause of hospitalisation and death in many

countries of Asia and the Americas. In July 2000, an outbreak of clinically suspected DHF (not confirmed by virus isolation) suggested by serological evidence, occurred in Dhaka, for the first time in Bangladesh. Sporadic cases are reported from different parts of the country. Thus, an attempt is made to review the current knowledge and experience regarding this emerging dengue infection and their management.

Bangladesh perspectives

Southeast Asia (SEA) is regarded as home of dengue viral diseases. And after the Second World War the periodic DHF epidemics have emerged as an important cause of morbidity and mortality in many countries of SEA. Interestingly, no major epidemic of DHF occurred in Bangladesh in the past. In 1964, dengue serotype 3 was responsible for classical dengue fever in Dhaka (Dhaka fever) and DHF was reported for the first time in Calcutta in India in that year. Apparently, a small outbreak of few cases of clinical DHF was reported in 1968 in an area of Bangladesh close to Myanmar. In 1996 and 1997 multiple dengue serotypes (dengue 2, 3 and 4) were detected for the first time to cause dengue fever in Chittagong, Bangladesh. In 1999, an outbreak of dengue fever with few unconfirmed cases of DHF was reported in Dhaka city, Bangladesh as suggested by positive serologic evidence. The exact dengue situation in Bangladesh is difficult to determine because of lack of facilities for virus culture and other methods for detection of viruses and their serotypes in the past.

Clinical approach to recognise dengue viral disease patterns

It has been observed that all dengue infections are not expressed clinically as symptomatic cases and a significant number of infected humans remained asymptomatic or minimally symptomatic for a short period of time. In a prospective study in Thailand, it was observed that 87% of 103 school children infected during the study period by dengue virus were either asymptomatic or minimally symptomatic being absent for a day from the school, 4% and 9% had DF and DHF, respectively. And the majority (78%) of DHF cases required hospitalisation for treatment and pre-existent dengue antibody was a significant risk factor for development of DHF. The clinical presentation depends on age, underlying diseases and immune status of the host and virus strain. The characteristics of different categories of common dengue diseases are summarized in Table 1.

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Table 1. Patterns of Dengue diseases

Syndrome	Clinical symptoms & signs	Haemorrhage	Laboratory results
Undifferentiated Fever	Fever, mild gastrointestinal or respiratory symptoms	TT +/-, bleeding + or -	Platelet: normal Hct: normal
Dengue Fever*	Fever, pain (headache, arthralgia, myalgia, eye pain) rash, gastrointestinal symptoms	TT +/-, bleeding + or -	Platelet: ↓ or normal Hct: normal
DHF	As above symptoms, haemorrhage, plasma leakage symptoms (pleural effusion, ascites) and thrombocytopenia ($< 100,000 / \text{cm}^3$)	TT + or -, bleeding- or +	Platelet: ↓ Hct: ↑ (by 20% or more)
Grade I		TT + bleeding-	same as above
Grade II		TT +, Spontaneous bleeding +	same as above
DSS			
Grade III	Circulatory failure manifested by cool, clammy skin, restlessness, tachycardia, ↓ BP, narrow pulse pressure ($\leq 20 \text{ mm Hg}$)	TT + or -, bleeding + or -	same as above
Grade IV	Profound shock indicated by no detectable pulse and BP	TT + or -, bleeding + or -	same as above

DHF = Dengue haemorrhagic fever, DSS = Dengue shock syndrome, TT = Tourniquet test

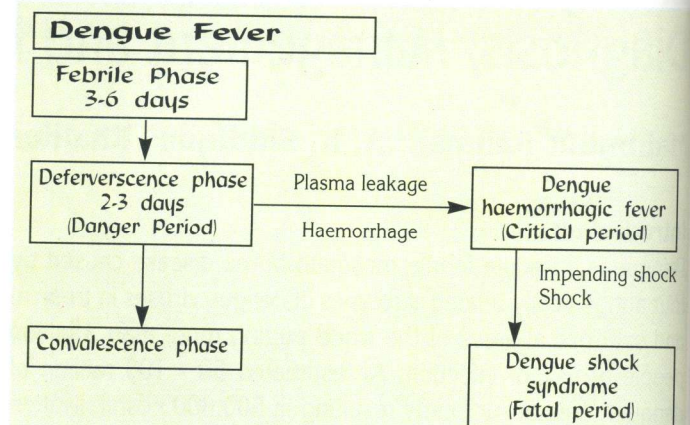
#Other severe dengue syndromes include encephalopathy, hepatic damage, and cardiomyopathy. *Dengue fever may present with severe haemorrhage.

Some dengue infections result in DHF, a syndrome that in its most severe form can threaten the patient's life, primarily by plasma leakage through increased vascular permeability leading to hypovolemic shock usually around defervescence phase (Figure 1). Inflammatory response to dengue infection produces vasculopathy. Extravasation occurs through endothelial gaps, without inflammation and necrosis of capillary endothelial cells resulting in haemoconcentration, pleural effusion, ascites, hypoproteinemia, hypoalbuminemia. The haemorrhagic phenomenon in dengue infection is complex and not well understood. Reduced formation, function and survival of platelet, action of cytokine, vascular injury and consumption coagulopathy may play role in the causation of bleeding manifestation.

Danger period (24-48h, time for development of DHF or DSS): needs observation, clinical and laboratory monitoring for prevention of severe disease.

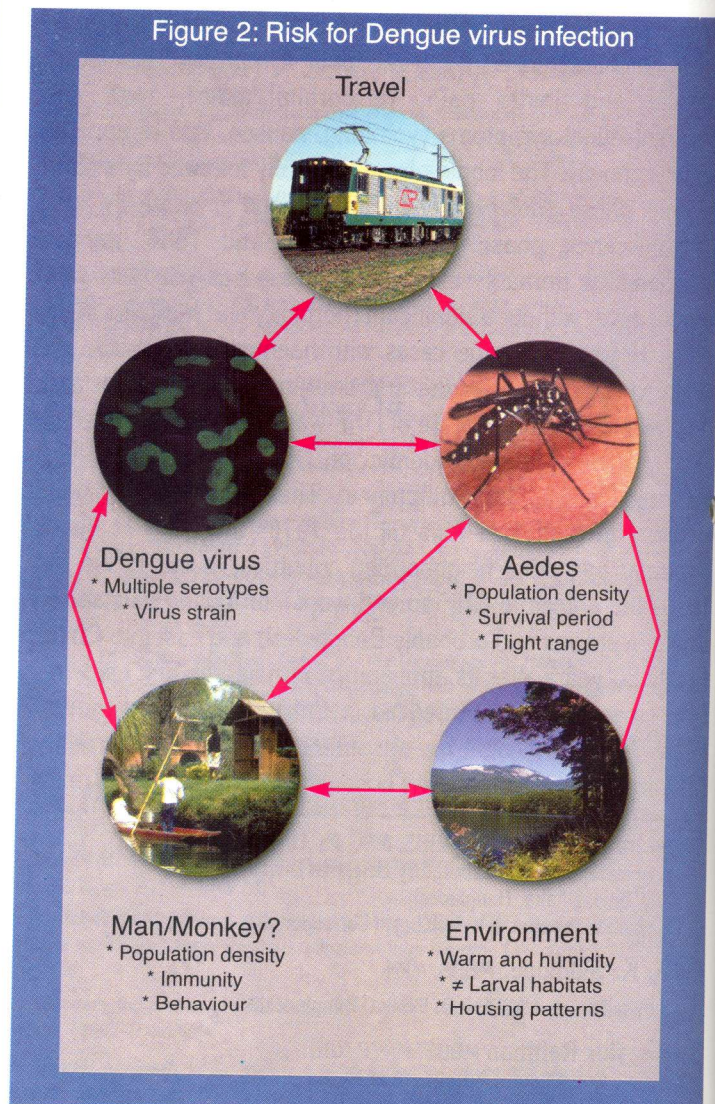
Critical period (time for development of DSS): needs above and require hospital care in outpatient or inpatient for prevention, early recognition and treatment of shock.

Fatal period (time for death, 12-24h): needs intensive treatment of hypovolemic shock, nursing and monitoring in special dengue care unit.

Figure 1 : Dengue fever leads to the development of DHF and DSS

Rick factors for dengue infections appear to be many, however reinfection of an area with *Aedes aegypti* and introduction of a new serotype where population's immunity is low are important contributing factors.

Figure-2 shows the interaction of different risk factors in the occurrence of DF.

Figure 2: Risk for Dengue virus infection

Laboratory diagnosis of Dengue infection

Confirmatory laboratory diagnosis of dengue infection include 1) virus isolation 1) detection of specific viral antigen or 3) dengue viral RNA and 4) demonstration of rising titre (4 fold or more) of dengue specific-serum antibodies (Table 2). Laboratory diagnosis is essential for patients and may be necessary for public health surveillance and medical record.

Virus isolation

Isolation of virus is the most definitive approach and is 50% sensitive with ace phase serum in tissue culture after 7 days of incubation. Viremia usually remains for 5 days after onset of symptoms and cleared rapidly with the appearance of antibody. After a week of incubation, cell cultures are stained with fluorescein-conjugated polyclonal antibody to detect virus isolates, and then serotyped with monoclonal antibodies in indirect fluorescent antibody test.

Serological diagnosis

It depends on the detection of presence of dengue-specific IgM or rise in IgG antibody titre in paired acute and convalescent phase sera by enzyme-linked immunosorbent assay (ELISA). The concern is many flavivirus such as Japanese encephalitis, West Nile, tick-borne and St. Louis viruses share group antigens with dengue virus that can cross-react in serological test making results less specific (false positive). IgM antibody becomes detectable in 90% of patients by the sixth day of illness by capture ELISA (MAC-ELISA) and may be detectable for a mean of 60 days. With a single acute phase serum after sixth day, MAC-ELISA has sensitivity of 75%. With paired sera it increased to 95%. IgM negative results on acute phase samples cannot exclude the diagnosis of dengue and convalescent serum should be collected. The IgG antibody appears by fifth day after onset of symptoms in primary dengue. Titre rises slowly for some weeks and then remains detectable for many years. IgG titres rise rapidly in secondary infection in a few days. Indirect ELISA is used to detect IgG. In dengue endemic region high rate of IgG positivity makes analysis of paired sample critical because the presence of IgG antibody in a single serum sample has no clinical significance.

Reverse transcriptase polymerase chain reaction (RT-PCR)

It may be used to detect all four serotypes of viruses and may shorten the detection time compared with viral culture. A multiplex PCR alone or followed by a nested PCR is commonly used in a single tube using four sets of primers. It can detect viruses in samples inactivated by improper storage or containing neutralizing antibody.

Haematological, biochemical and other tests

WBC is normal initially, but leucopenia is common with neutrophil predominating. At the end of febrile phase leucopenia is observed with low neutrophil and lymphocytosis with atypical lymphocytes.

Platelet: 100, 000 / cm³ on 3rd – 8th day

HCT: increases with plasma leakage in DHS by 20% or more

Mild albuminuria or positive occult blood test

Serum: protein, albumin, C3, C5, prothrombin and fibrinogen may

decrease and SGPT, SGOT may increase in DHF / DSS patients

Prothrombin time and partial thromboplastin time may increase.

Table 2. Laboratory Diagnosis of Dengue Viral infections

Virus isolation	Serum, plasma, WBC or autopsy sample	Mosquito/ mice inoculation Mosquito cell culture: C6/36 or AP-61 Mammalian cell: VERO, LLC-MK2	Antigen detection by serotype-specific immunofluorescence head squash CPE effects and antigen detection
Antigen detection	Tissue samples Serum	Immunofluorescence or Immunoperoxidase test ELISA	
Antibody detection IgM, IgG	Serum, plasma (Acute and 14 day, paired)	MAC- ELISA for IgM Indirect ELISA for IgG	a) Four fold rise in anti-dengue antibody titres b) Anti-dengue antibody ≥ 40 units c) IgG $\geq 163,840$ units for secondary infection d) IgM / IgG ratio ≥ 1.78 for primary infection, less for secondary infection
RNA detection (cDNA)	Serum, CSF or autopsy sample	RT-PCR	Detects virus and serotypes

Other serological tests include hemagglutination and neutralization tests. The results of combined IgM and IgG raid test are difficult for interpretation. The rapid immunochromatographic test may be useful for serosurveillance in association with ELISA.

Clinical Management of Dengue

There is no specific treatment of dengue viral diseases. The management is symptomatic and supportive. However, effective case management include following requirements:

- Well-trained Physicians, Nurses
- Reliable laboratory facilities
- Adequate blood supply
- Functioning pharmacy
- Dengue treatment unit during epidemic

Dengue fever (Classical) - Home management

It is symptomatic and supportive

- Rest
- Analgesics
- Antipyretics and sponging with tap water to keep temperature $<39^{\circ}\text{C}$. Use only paracetamol, never use aspirin nor non-steroidal antiinflammatory drugs.
- Mild sedatives may be needed
- Oral fluids such as oral saline, fruit juice and soft drinks are very useful and should be used and more so in patients with diarrhoea and vomiting.
- Monitoring of patient is the most important measure for the prevention, early diagnosis and treatment of DHF and DSS. It includes clinical and laboratory components:

Clinical monitoring :

Fever - very high fever cases frequently develop DHF

Bleeding manifestations

Urinary output

Level of consciousness

Blood pressure (pulse pressure)

Laboratory monitoring: HCT

Platelet count

TC, DC of WBC, Hb%

Alarm signs develop usually 3-6 days after onset of symptoms. If alarm signs are noticed during monitoring of patient, the patient may require hospitalisation.

Alarm signs are:

- Drop in BP
- Drop in platelet
- Increase in HCT
- No urine in last 4-6h

DHF Grade I & III

Patients with fever, platelet count ($<100,000 / \text{cm}^3$), increased HCT ($\geq 20\%$) and minor bleeding including a positive TT test may be treated in outpatient observation clinic or may require hospitalisation.

Treatment in Observation ward or OPD like a Diarrhoea Treatment Corner

Fluid therapy: isotonic fluid, half strength saline in Glucose or Ringer's lactate for 24 – 48 h and plenty of fluid orally.

Antipyretics and sponging to keep temperature $< 39^\circ \text{C}$.

Monitoring: Clinical and laboratory, input-output and vital signs for prevention, early diagnosis and treatment of DSS cases.

Hospitalisation of dengue patient: When?

DF or DHF patient not improving during observation and has any one of following needs immediate hospitalisation:

- a) Drop in BP
- b) Platelet count $< 50,000$
- c) Increase in HCT ($>20\%$) or rising HCT
- d) Major haemorrhage
- e) Patient with altered consciousness or convulsion
- f) All DSS patients (DHF grade III & grade IV)
- g) Patient with severe abdominal pain with hepatomegaly

Principles for the optimum treatment of severe dengue diseases (DSS / DHF)

Fluid therapy (replacement of plasma loss): Correct loss immediately ($10 - 20 \text{ ml} / \text{kg} / \text{hr}$) as required and maintain it for 2 to 4 days. Fluid replacement is performed as in the case of diarrhoeal patient. Replace loss immediately as bolus and then maintain it usually for 24 to 72 h depending on clinical response. The amount of fluid is usually daily maintenance plus 5% of body weight.

Type of Fluid: isotonic crystalloid fluid (half strength saline in glucose or Ringer's lactate or 5% dextrose in aqua) and Dextran 40 in severe cases if no improvement occurs with crystalloid fluid. In severe cases, initial hydration with Dextran 40 provides better results.

Electrolyte and metabolic corrections: Fresh Blood is indicated in severe bleeding, in refractory shock (no improvement with crystalloid or colloidal fluid) and DSS with DIC. Only 15% - 20% of DSS patients may require blood.

Platelet concentrate usually offers no benefit in case of thrombocytopenia as shown by different studies.

Steroid and vesopressive drug are not useful

No role of antibiotics and vitamin C

Antiviral drugs are not effective

Monitoring of patients: Clinical and laboratory, input-output and vital signs for prevention of death.

Intensive care and treatment are required for the first 48-hour for preventing case fatality in DSS as most case-fatality occurs during the first 12 – 24 h.

Prospects for control

Vaccine Development

Live attenuated vaccine containing four dengue serotypes, developed by Mahidol University, Thailand, are undergoing commercial production. Preliminary clinical studies suggest that they can be safe and immunogenic. Concerns remain regarding the conversion to virulent strain. Inactivated vaccine candidates are safer and the immunogenicity of formalin-inactivated dengue 2 virus is encouraging. However, the cost of vaccine appears to high because of insufficient and slow growing nature of dengue virus in tissue culture. The recent exciting development of complete infectious cDNA clones of dengue virus holds a great promise as the basis for a dengue vaccine.

Vector control

Control of dengue currently depends on controlling its vector *Aedes* mosquito (*Ae aegypti*, *Ae albopictus*). *Aedes* is peridomestic mosquito with a short flight range (100 yards) and breeds exclusively in artificial habitats such as water-storage container and discarded items that collect rainwater and particularly rainwater-filled tree-holes. Elimination of these peridomestic larval sources is the most effective way to control mosquitoes that transmit dengue. Space spraying with insecticides to kill adult mosquitoes is usually ineffective. The aerosols are particularly recommended for emergency control during epidemic transmission as part of an integrated vector elimination effort including environmental management, source reduction and use of larvicides.

Community participation

In recent years, the emphasis has shifted towards community-based approaches, based upon health education and individual responsibility to eliminate peridomestic mosquito larval habitats. However, it takes long time to control wide geographical area.

Protection of host from mosquitoes bites

The bites can be avoided by covering body with clothes and shoes, using repellents such as DEET (30%) and coils. It may be remembered that the peak biting time is early morning and late evening, though it can bite any time. Visiting a dengue endemic area is a risk factor for dengue infection. Thus, special care must be taken to avoid this infection. Biting of an infected person (patient) must be prevented by keeping in mosquito net and in relatively mosquito-free area to prevent transmission and spread of diseases in order to break the cycle of mosquito-human-mosquito. It is wise to use mosquito nets to babies, old people and others who may rest during the day.

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Chancroid- The Most Frequent Cause of Genital Ulcer Disease.

A prospective study by using PCR assay.

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ABSTRACT

Aim : Since the etiology of genital ulcer disease (GUD) in Bangladesh is based on clinical ground and syphilis serology only, the present study was designed to provide information on the etiology of GUD by using recommended laboratory methods.

Methods : To demonstrate ulcer etiology 98 male patients with clinically diagnosed GUD reporting at DMCH Bangladesh were prospectively studied for serologic evidence of syphilis (RPR & TPHA, *T. pallidum* IgG and IgM antibodies), culture and PCR proven chancroid and PCR proven genital herpes. The outcome of laboratory diagnosis were compared with the clinical diagnosis.

Results : A definite microbial etiology of 88 infection in 72 of the 98 patients evaluated was found. *H. ducreyi* (65%), *herpes simplex* (13%) and *T. pallidum* (11%), alone or in combination, were the most frequent diagnosis, whereas 27% had no laboratory diagnosis. Seventeen patients (65%) of the latter group had clinically genital scabies with high eosinophil count, seems to be responsible for ulcer infection. Excluding the mixed infection, the sensitivity of the clinical diagnosis of chancroid was 30.6% and syphilis was 57%. The number of single herpes infection was too small for evaluation. Laboratory proven chancroid was frequently observed among the remaining clinical diagnosis.

Conclusion : All GUD patients should be treated for chancroid including all those having reactive syphilis serology.

INTRODUCTION

Genital ulcer disease (GUD) constitute a major risk factor for the sexual transmission of HIV[1-2]. In many developing countries syphilis, chancroid and genital herpes was the most frequent diagnosis among the patients with GUD by using recommended laboratory methods [2-6]. Genital Scabies "Pyogenic infection", syphilis and chancroid have been claimed to be major causes of GUD in Bangladesh [7-9]. Diagnosis is almost

exclusively based on clinical grounds and syphilis serology only. It was reported that the clinical diagnosis can be made with reasonable certainty only for a minority of cases even if performed by experienced clinician [10-12].

Reactive syphilis serology (RPR & TPHA) showed 83-90% specificity and 66-72% sensitivity when taking PCR as the standard for diagnosis [13-14], so there exist a chance of overestimation or missing of active syphilis. Use of culture for laboratory confirmation of chancroid has high specificity and low sensitivity in terms of gold standard methods [15]. Since nutrition requirements of *H. ducreyi* are very complex, lack of essential substance in the culture media may have been responsible for the poor yield of *H. ducreyi* [16]. Therefore when a culture of *H. ducreyi* is negative, there exist a chance of false negative results [17].

PCR technique for the diagnosis of syphilis, chancroid and herpes has high specificity and sensitivity and used as a gold standard for assessing the validity of a diagnostic procedure [13,15]. In this study the PCR technique were used for the detection of *H. ducreyi* and *herpes simplex virus*. The aim of the present study was to provide information on the etiology of GUD in Bangladesh by using recommended laboratory methods.

PATIENTS AND METHODS

Patients

The study was carried out at the Skin and VD outpatient Department of Dhaka Medical College Hospital and at the Laboratory Sciences Division of ICDDR,B in Dhaka, Bangladesh through out the months of March and April, 1999. A total of 98 patients with GUD were selected for the study. All subjects were male and at least 15 years of age. Each patient was ensured confidentiality and anonymity and asked to participate in an interview regarding socio-demographic variables, sexual behavior and information was collected about the use of the medicines, the presence of symptoms such as pain, itching, recurrent character of the lesion, the presumed source of infection and a history of STI in the past. All patients under went a physical examination of the external genitals, the inguinal regions and the rest of the body.

Clinical diagnosis

The etiological diagnosis based on clinical sign complex attributed to syphilis (painless, indurated, clean-based

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ulcer) chancroid ulcer (a deep, undermined purulent ulcer), genital herpes ulcer (multiple, grouped, shallow, tender ulcer) and genital scabies ulcer (multiple itchy purulent, tender ulcers, and/or presence of burrow especially on the genitalia and adjacent areas and characteristic distribution of scabies lesions else where in the body). Donovanosis* was considered when the lesion had a beefy aspect.

Laboratory diagnosis

Isolation of *H. ducreyi* :

For the isolation of *H. ducreyi* a cotton tipped swab rolled in the ulcer, after cleaning with the back of a hemostylet, and plated on-

- Mueller-Hinton medium (Becton Dickinson, Cockeysville, Maryland, USA), supplemented with 1% hemoglobin (Becton Dickinson), 1% Iso VitaleX (Becton Dickinson), 5% sterile fetal calfserum (Life Technologies Inc, N.Y. USA) and 3 µg of vancomycin/ml;
- GC-agar base (Becton Dickinson) enriched with the same ingredients.

All plates were incubated for seven days at 33°C in a candle jar. Presumptive identification of *H. ducreyi* was based on the typical colonial morphology, Gram staining, a negative catalase test and a positive oxidase test with tetramethyl-p-aminophenylene diamine. All strains were tested for the presence of a β-lactamase with the chromogenic cephalosporin test (Nitrocefin.R Becton Dickinson).

Detection of *H. ducreyi* by PCR technique:

A dacron tipped swab was subsequently rubbed against the ulcer base and stored in a sterile 1 molar phosphate buffered saline solution (PBS; 50 mM sodiumphosphate, 0.15M sodiumchloride; pH 7.5), but without sodium chenodeoxycholate [18] and stored at -70°C until shipped to the Laboratory. Three different primers were used for the detection of the *H. ducreyi* genome [19-21]. Only samples giving a positive result with three primers were considered as being positive.

Detection of *herpes simplex* virus by PCR technique :

Detection and typing of *herpes simplex* virus was performed with two different primers [22]. Only samples giving a positive result with two primers were considered as being positive and further typing of *herpes simplex* virus was done according to Kimura et al. [23]

Serology for syphilis:

For the diagnosis of syphilis, serum specimens were tested with the rapid plasma reagin test (RPR nosticon, Organon Teknika, Turnhoul, Belgium) which was titrated till the end point, as well as with the *T. pallidum* haemagglutination assay (TPHA nosticon, Organon

Teknika). *T. pallidum* IgG and IgM antibodies were detected with an ELISA technique (*Treponema pallidum* IgM EIA, *Treponema pallidum* IgG Comfort EIA, Meddens Diagnostics, Brummen, The Netherlands). Patients were considered as having primary syphilis if the RPR was reactive in the presence of a positive TPHA test and in all cases where IgM antibodies to *T. pallidum* were diagnosed. All patients with a positive IgM test were screened for the presence of the rheumatoid factor (Serodia-RA, Fujirebio, Tokyo, Japan).

Detection of *C. donovani*:

With the back of the haemostylet smear from the ulcer was prepared for specific staining and microscopy. Total and differential WBC count were performed in all cases. Microscopic detection of the scabies mite was not performed since it is not expected to be fruitful in scrapings of heavily infected lesions.

RESULTS

Socio-demographic data: Summarized in table-1.

The mean age of the patients was 24 years ± 8.5 years. A majority of the GUD patients were unmarried (72.4%). Most patients belonged to the lower socioeconomic strata of Dhaka and were small traders, rickshaw pullers, drivers, unskilled daily wagers or factory workers. However 20% of patients were students. A large proportion of patients reported of having multiple sexual partners. Forty-six percent of patients indicated sex worker as source of infection and 56% (14/25) of the married men reported recent sexual contact with commercial sex worker. Fourteen percent had history of STD.

Clinical findings : Depicted in table -2.

Ninety-six patients were circumcised. Ulcers were localized on the glans or skin of the penis or on the scrotum, only one patient had anal and peri-anal. Twenty nine (29.6%) patients had a single ulcer, 14 (14.3%) had 2 ulcers and 55 (56.1%) had more than 2 ulcers. Five (5.1%) men had balanitis, 28 (28.6%) inguinal lymphadenopathies, 5 of them with buboes. One patient had generalized chicken pox and 45 (45.9%) patients showed scabies lesions elsewhere on the body. More than half of the patients (54%) had waited more than two weeks before attending the out patient department. The clinical diagnosis was genital scabies (n=49), chancroid (n=30), syphilis (n=12), genital herpes (n=3), traumatic ulcer (n=2), donovanosis (n=1) and chickenpox (n=1).

Laboratory diagnosis : Represented in table -3.

A definite microbial etiology of 88 infection was found in 72 of 98 patients evaluated. *H. ducreyi* was isolated

from 22 patients, 42 additional *H. ducreyi* infection being discovered by the PCR technique. Four of the five (80%) patients with inguinal buboes had a positive *H. ducreyi* PCR test and all were negative for any other laboratory diagnosis. All 22 culture positive samples were PCR positive. Therefore laboratory diagnosis of chancroid was confirmed in 64 (65%) cases with GUD, among them 49 had chancroid infection. *H. Ducreyi* were isolated or detected in 6 of 12 (50%) cases which were clinically diagnosed as syphilis, in 30 of 49 (61%) cases which were recognized clinically as genital scabies and in 2 of 3 (67%) cases of clinically diagnosed genital herpes. One of the patients with a traumatic ulcer was culture and PCR positive for *H. ducreyi*. The patient with generalized chicken pox had chancroid and the patient with clinically diagnosed donovanosis harbored chancroid as mixed infection with genital herpes. After exclusion of mixed infection, not expected to be recognized clinically, the sensitivity of the clinical diagnosis of chancroid was 30.6% (15/49). Culture of *H. ducreyi* had 34.4% sensitivity when taking PCR as the standard for diagnosis.

There were 11 (11.2%) serology proven syphilis, among them 9 patients showed a reactive RPR test in the presence of a positive TPHA test. Two patients negative for RPR (up to titer 1:32) and *T. pallidum* IgG antibodies, were positive for TPHA and IgM. Both patients were negative for the RA factor and considered as having active syphilis. Single syphilis infection were detected in 7 (7.1%) cases. Excluding the mixed infection, the sensitivity of clinical diagnosis of syphilis was 57% (4/7).

Genital herpes were detected in 13 (13.3%) patients. Type-2 infection observed in 7 (7.1%) patients, type -1 in 4 (4.1%) patients and 2 patients harbored a mixed (type -1 and type-2) infection. The single genital herpes infection was detected in one patient which was clinically diagnosed as a traumatic ulcer. Remaining all 12 infection represented as mixed infection with chancroid and only one with syphilis.

Table 1: Socio-demographic profile and sexual risk behavior of the GUD patients DMCH, Bangladesh.

Characteristics	N=98	%
Mean age (years $\pm$ SD)	24 $\pm$ 8.5	
Civil Status		
Married	25	(25.5)
Unmarried	71	(72.4)
Divorced	2	(2.0)
Socio-Economic Status		
Lower	54	(55.1)
Middle	38	(38.8)
Higher	6	(6.1)
Sexual Partner		
Single	1	(11.2)
Multiple	72	(73.5)
No	15	(15.3)
Sex worker as source of infection		
Married men	14	(56.0)
Unmarried / separated man	31	(42.5)
History of sexually transmitted infection	14	(14.3)

Table 2 : Clinical data of 98 genital ulcer patients DMCH, Bangladesh.

Characteristics	N=98	(%)
Duration of lesions		
< 8 days	25	(25.5)
8-14 days	20	(20.4)
> 14 days - 1 month	27	(27.6)
> 1 month	26	(26.5)
Number of ulcers		
Single	29	(29.6)
Two ulcers	14	(14.3)
> 2 ulcers	55	(56.1)
Complaints of		
Pain	72	(73.5)
Itching	80	(81.6)
Recurrent lesions	8	(8.2)
Urethral discharge	5	(5.1)
Dysuria	39	(39.8)
Antibiotic use before consultation		
Oral antibiotics	37	(37.8)
Local treatment	44	(44.9)

Table 3 : Association between clinical and laboratory diagnosis.

Clinical diagnosis	Laboratory diagnosis					
	N=98	Chancroid N=49	Syphilis N=7	Herpes N=1	Mixed infection N=15	No diagnosis N=26
Scabies	49	26	2		4 †	17
Chancroid	30	15			8 ‡	7
Syphilis	12	5	4		1 †	2
Herpes	3	1	1		1 †	
Donovanosis	1				1 †	
Other ¶	3	2		1		
Mean % eosinophils	$\pm$ SD	43 $\pm$ 3.3	3.4 $\pm$ 2.1	3.0 $\pm$ 0	3.3 $\pm$ 2.4	7.0 $\pm$ 4.8
¶ traumatic (n=2), chicken pox infection (n=1)						
‡ chancroid, herpes						
† chancroid, herpes (n=4), chancroid, syphilis (n=3), chancroid, herpes, syphilis (n=10)						

Laboratory proven mixed infection was observed in 15 cases. Chancroid detected in all cases, genital herpes in 12 cases and syphilis in 4 cases. The 26 cases of GUD with no demonstrable ulcer etiology included the 17 cases of clinically diagnosed genital scabies. The mean leucocyte count was 10357/cmm. The mean percentages of eosinophil was 4.0 $\pm$ 3.0 among the patients with proven infections and 7.1 $\pm$ 5.0 in patients with no laboratory diagnosis. Among the latter group 17 patients with clinically diagnosed scabies had the highest eosinophil level (8.6 $\pm$ 1.2)

DISCUSSION

This study confirmed chancroid as the leading cause of GUD in Bangladesh. Similar observation were drawn in many developing countries where chancroid was the most frequent diagnosis [2-3]. The relative frequency of

chancroid and syphilis is in contrast to our previous observation [9] and confirmed the lack of accuracy of the clinical etiologic diagnosis of genital ulcers [10-12]. The socio-demographic profile and sexual risk behavior described earlier [9] remained unchanged in our present study.

A low frequency of syphilis raises a dilemma in the etiological ranking of GUD in Bangladesh. The rate of syphilis observed in our study may not very precisely represent the actual prevalence of syphilis in the community as some patients with GUD reporting to the primary health care providers erroneously consider all cases of genital ulcers as syphilis and treat them. The wide spread use of antibiotics before attending the clinic may have prevented the development of *T. pallidum* antibodies, on the other hand, the sensitivity of syphilis serology (RPR & TPHA) indicating that some infections were missed and leading to underestimation of syphilis.

The number of single herpes infection was too small for evaluation. *Herpes Simplex* virus may secondarily invades the pre-existing genital ulcers without altering the clinical sign complex of primary infections. On the other hand the spontaneous resolution of genital herpes ulcer prevents many patients from seeking treatment. Perhaps these patients come to the clinic with concomitant infection that does not heal inherently and difficult to recognize clinically. These might be the interpretations for most of the genital herpes patients with mixed infection.

Sixty five percent (17/26) of the patients with no laboratory diagnosis had clinically genital scabies and significantly high eosinophil count. Therefore genital scabies as single infection seems to be responsible for the ulcer infection among this group. However in the remaining 65% (32/49) clinically diagnosed genital scabies cases it cannot be excluded that pre-existing genital scabies lesions became secondarily infected with *H. ducreyi*, *T. pallidum* or *herpes simplex* virus resulting in a clinical picture of secondarily infected scabies. A high eosinophil count would be expected which was not observed among this group. Therefore such mixed infection remains unproven.

The high prevalence of chancroid and their presence in the most of the clinically diagnosed genital scabies, syphilis and genital herpes cases is the most striking finding of the present study. The study showed point prevalence of different etiologic causes of GUD and stressed on future study on large sample size representative of GUD population of Bangladesh. Since the sensitivity of the clinical diagnosis of chancroid is very low, many infection are missed, on the other hand

as the culture of *H. ducreyi* had low sensitivity there exist a chance of many false negative results. Therefore it will be justifiable to treat all GUD patients for chancroid including all those having reactive syphilis serology.

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Polycystic Ovary Syndrome (PCOS)

Kohinoor Begum¹, Begum Maksuda Farida Akhtar²

INTRODUCTION

PCOS is a complex reproductive disorders in women. In 1930, it was first defined by Stein and Leventhal.

Clinically PCOS is the younger women's problem of irregular menstruation, amenorrhoea or oligomenorrhoea, sub-fertility, hirsutism and include potential long-term metabolic and cardiovascular consequences.

There are links between PCOS and endometrial carcinoma, obesity, cardiovascular disease and diabetes. So it is evaluated and treated by a team of specialists like- Obstetricians and Gynecologists, Cardiologists, Medical endocrinologists, Reproductive endocrinologists, Dermatologists and Paediatricians. Because of increasing life expectancy, symptoms related to PCOS are now evaluated and treated both for short-term relief and for long term sequels.

The prevalence of PCOS cannot be determined with precision. Based on endocrine characteristics, prevalence of PCOS is 3% and based on Ultrasonic morphology, the prevalence is 22% and clinically it is 5%.

CLINICAL FEATURE

Affected age group between 15-30 years. Patient with PCOS seeks health care for three major reasons-

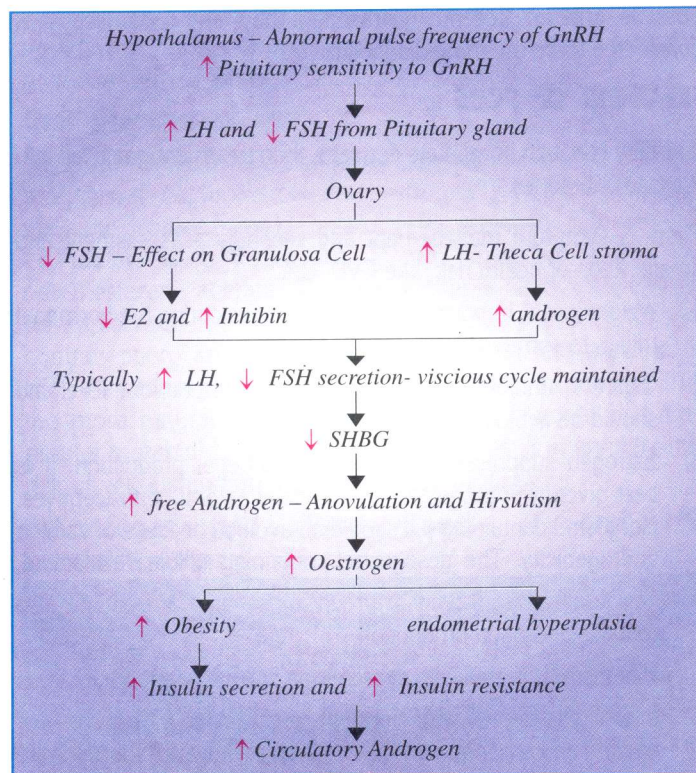
1. Sub-fertility-mean incidence is 74%.
2. Menstrual irregularity-DUB-29%, Amenorrhoea-51%.
3. Androgen excess-Hirsutism-69%, Virilism-21%.

In 50% cases, slight HTN, obesity, and in late age patient comes with Type -II diabetes and in 50% cases bilateral enlarged ovaries are seen.

PATHOPHYSIOLOGY

The fundamental defect of PCOS remains unknown. The endocrinologic effect of PCOS produce a visicious cycle of events as shown in the flow chart.

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METABOLIC ABNORMALITIES OF PCOS

1. Obesity- The cause of obesity in PCOS is unknown. Patients have slow metabolism results decrease use of energy. Weight loss is difficult with diet and exercise.
2. Increased Insulin Resistance- Here insulin receptors are normal and do not have genetic mutation. But defect is at post receptor level e.g. activation of glucose transporter and transport of glucose into the cell. There may be glucose intolerance and type II diabetes. The patients may exhibit greater rates of gestational diabetes.
3. Others- Patients have increased Blood pressure, Serum total cholesterol, increased LDH, TG but low HDL. They are more prone to produce cardiovascular diseases.

DIAGNOSIS

Investigations-

1. Transvaginal Ultrasonography especially in obese patient.
2. Serum Hormone Level- ↑ LH, LH: FSH is > 3:1, reverse E₂: E₁.
3. Abnormal serum lipid profile- ↑ TG, ↑ Cholesterol, ↑ LDH, ↓ HDL.
4. Laparoscopy- Bilateral polycystic ovaries, capsule thick with pearly white.
5. Histology of ovarian tissue- there is thickening of Tunica albuginea. The follicles are at varying stages of maturation and theca cell hypertrophy.

DIAGNOSTIC CRITERIA

54 experts of National Institute of Health from different parts of the World have agreed that no single of criteria could be endorsed for definite or probable diagnosis. Factors such as Insulin resistance, ↑ LH: FSH, polycystic ovary on Ultrasonography is considered to be possible criteria. Recently Ultrasonography and laparoscopy is considered to be the most diagnostic.

TREATMENT OF PCOS

If fertility is not an immediate concern, then treatment goals fall into 2 broad categories –

First– is symptom management and secondly – assessment and amelioration of health risk, like CVD, DM.

1. Weight loss is important and will help in restoring the hormonal milieu to some extent.
2. Cigarette smoking raises DHEA and androsteredione level and should be avoided.
3. Estrogen suppresses androgen and adrenal production. It is best given with progesterone cyclically as oral contraceptives. Norgestrel containing pill should be avoided because of its high androgenicity. The desogestrel-containing pill is best suited.
4. Dexamethasone 0.5mg or prednisolone 5mg at bedtime also reduces androgen production.
5. Hirsutism is treated with cyproterone acetate or spironolactone.
6. Infertility is treated with clomiphene citrate. In 80% cases they ovulate and among them 40% conceive. However abortion rate is 25-40% is due to corpus luteal phase defect manifested by clomiphene. Hyper stimulation syndrome common in PCOS.
 - ** Clomiphene with dexamethasone increases the ovulation rate.
 - ** In clomiphene-failed group, ovulation can be induced with FSH, LH or GnRH analogues.
7. Surgery is reserved for those in whom – medical therapy fails or hyper stimulation occurs.

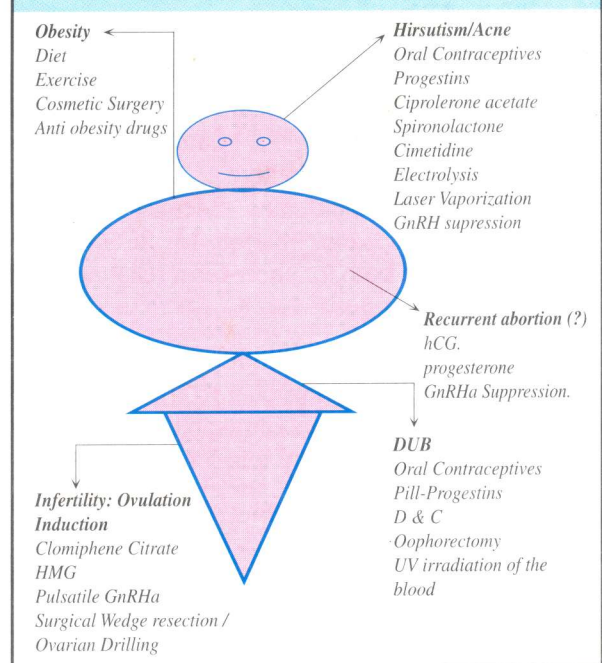
Surgery comprises laparoscopic multiple punctures of the cysts with electrocautery or laser. Wedge resection is now avoided on account of postoperative ovarian adhesions and continued infertility

8. Treatment of hyper insulinemia, Insulin resistance and glucose intolerance in PCOS-
 - a) Diet with exercise – there is no effective treatments that result in permanent weight loss. About 90% to 95% of obese patient who have a weight decrease later gave a relapse. Weight loss can improve the fundamental aspect of the –
 - (i) Endocrine syndrome of PCOS & result in lower circulatory androgen level.
 - (ii) Decrease level of circulating insulin.
 - (iii) Decrease level of unbound testosterone by increasing SHBG.

b) Drug–

Antidiabetic drugs/Insulin-sensitizing agents			
	Troglitazone	Metformin	Chlorpropamide Tolazamide, Glipizide
Drug class	Thiazolidinedione	Biguanide	Sulfonylurea
Site of action	Adipocyte and muscle	Liver	Pancreas
Primary effect	Improves insulin action	↓ Glucose production ↓ glucose uptake	↑ Insulin secretion
Adverse events	Liver damage (rare)	Abdominal discomfort, lactic acidosis. (rare)	Hypoglycemia

Current treatment of PCOS according to presenting symptoms



SUMMARY AND CONCLUSIONS

A recommendation for the care of women with PCOS would include the following:

1. Careful monitoring of body weight with extra counseling to maintain normal weight.
2. Aggressive treatment of obesity.
3. Annual screening of all patient with PCOS for HTN.
4. Baseline screening for fasting lipid profile.
5. Screening of patient at rest for GTT.
6. Symptoms of cardiovascular disease should be regarded with a higher index of suspicion in the PCOS.

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Hormone Replacement Therapy (HRT)

L. A. Banu¹, Dipti Pramanik²

A WOMEN IN THE AUTUMN OF HER LIFE, DESERVES AN INDIAN SUMMER, RATHER THAN A WINTER OF DISCONTENT.

-ROBERT GREEN BLLATT.

Just over 100 years ago, when it was first realized that climacteric symptoms were related to ovarian failure, the first attempt at treatment involved the prescription of sheep's ovaries in a sandwich of unleavened bread [3]. In the affluent countries of the west, there are an ever increasing number of Hormone replacement therapy (HRT) preparation available.

But it is often difficult even for the menopause expert to decide what may be suitable for a particular individual patient, when prescribing HRT? What is the most suitable route of administration? The patients preference may be the most important determining factor.

Preparation of HRT are available for, delivery orally, transdermally, percutaneously, subcutaneous implant or vaginally or with an I.U.C.D. In addition, sublingual and intranasal spray options are being evaluated. In mainland Europe, injectable form of oestradiol are also available. At present in the UK, the only approved form of administration of testosterone to women is implantation. In reality, most women starting HRT- oral tablets will be the best option.

ORAL

Oral Oestrogen is the most suitable initial therapy for most women, in the UK, for women with a uterus who are taking HRT over 80% take oral therapy. Now we have a wide range of natural oestrogen preparation containing oestradiol, oestrone, conjugated equine oestrogens and the synthetic steroid tibolone, which has oestrogenic androgenic and progestogenic activity.

After oral administration of oestradiol, there is extensive metabolism in the wall of the small intestine, and further changes occur on reaching the liver, so that only about 10% reaches the systemic circulation as oestradiol and much larger proportion as oestrone, oestrone sulphate or oestradiol glucuronide. Following oral oestrone there is similar result in circulation but with any oestrogen preparation up to 90% of the administered dose may be inactivated before reaching systemic circulation. Thus the dose administered oestrogen has to be correspondingly higher than that given by non oral routes to achieve the same effective blood levels. This so called "first pass" effect constitutes the major difference between oral and non-oral administration of oestrogen and has various clinical

implication. In postmenopausal women who is not taking HRT oestrone is the dominant oestrogen and there is an oestradiol: oestrone ratio of about 0.2.

Oral preparation are-

Oestrone based (Harmogen), oestradiol based (2 mg progynova), conjugated equine oestrogen (0.625 mg premarin) tibolone (livial 2.5 mg). Oestriol (1mg ovestin), Kilogest (R)-28 tablets each containing 2 mg oestradiol and 1 mg norethisterone acetate. The semisynthetic oestrogen, ethinyl-oestradiol and mestranol, were developed primarily for oral contraception, and are generally considered less suitable for HRT. Mestranol and ethinylloestradiol are much cheaper than the more natural preparation but there is concern that their greater metabolic effect on the liver may result in an increased risk of venous and arterial thrombosis[11,12].

Advantages and disadvantages of oral HRT administration

Advantages	Disadvantages
* Easy to take, most people are used to swallowing tablets. * Tablets are usually cheaper than other routes of administration. * Good control due to short half life so can be withdrawn quickly. * Wide choice of preparation available.	* A high dose of oestrogen is required to overcome the extensive metabolism in the intestine and liver before reaching systemic circulation. * Wide variation in absorption and metabolism during the 1st pass effect of intestine and liver. * Alteration of some liver function and protein synthesis. * Oral oestradiol is mainly converted to oestrone. * Higher incidence of minor side effects than other routes. * Requires daily dosage. * All tablets contain lactose.

TRANSDERMAL OESTROGEN

Oestrogen is well absorbed through skin and subcutaneous fat as well as vaginal epithelium, nasal and sublingual mucosa. The main advantage of all these routes of administration is that metabolism in the liver and intestine is avoided. Pure oestradiol can therefore be administered directly into the systemic circulation and an oestradiol: oestrone ratio is similar to that found in premenopausal women.

Patches

The first skin patch Estraderm TTS Contains a reservoir of oestradiol with an alcohol solvent behind a rate limiting membrane and adhesive layer. Satisfactory circulating oestradiol levels are achieved but local skin reaction can be a

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troublesome side effect in upto 35% of women. Newer transdermal systems consists of a single transparent matrix with an adhesive layer which contains oestradiol.

The dose delivered is proportional to the surface area of the patch in contact with the skin. They cause less skin reaction and are cosmetically more acceptable than the alcohol containing reservoir patch. Combined oestrogen and progestogen patches are also available. Most patches have to be changed twice weekly.

Advantages and disadvantages of transdermal patches.

Advantages are - low dose pure oestradiol, avoids intestine & liver metabolism.

Physiological oestradiol : oestrone ratio, reduces serum triglycerides, fewer side effects.

Disadvantages - skin reactions, more expensive than tablets, not well tolerated in warm climates, variable absorption.

Gel

This mode of delivery is becoming increasingly popular. A preparation which involves the daily application of oestradiol gel on the skin is available. The standard manufacturers recommended dose is 5 gm cream containing 3mg of oestradiol daily. The method of administration gives a physiological serum oestradiol to oestrone ratio by bypassing the enterohepatic circulation. The daily application of gel requires a patient compliance either to arms or legs. A gel containing 1mg 17 beta oestradiol/gm gel has recently been introduced in the U. K.

Implants

Pellets of crystalloid oestradiol have been available for subcutaneous implant for over 50 yrs. Insertion of the pellets requires a minor surgical procedure which may be one reason for limited popularity, thought it is easy, takes 3-4 minutes and is safe. Pellets of oestradiol are available 25, 50 & 100 mg doses. The 50 mg dose is most commonly used for postmenopausal oestrogen replacement and given at 6 monthly intervals produces a circulating level of approximately 400 pmol/ L at one year. For the prevention of osteoporosis, a level of at least 300 pmol/ L is required and higher levels may achieve for greater replacement of bone.

The advantages and disadvantages of HRT implants

Advantages

Pure oestradiol,
Six monthly insertion,
High levels oestradiol in blood,

Avoids first pass effects,
Physiological oestradiol:
oestrone ratio,
Testosterone / 100mg can also
be given.

Disadvantages

Surgical procedure,
Unable to control absorption,
Risk of supraphysiological
blood levels,
Difficult to remove pellets,
Prolonged release
of oestradiol,
Risk of tachyphylaxis.

VAGINAL PREPARATION

Systemic therapy does not always produce an improvement in vaginal symptoms and for women with symptoms of systemic and local oestrogen deficiency, a combination of systemic and vaginal oestrogen may be necessary initially, until the vaginal epithelium has responded. Vaginal preparations are vaginal conjugated equine oestrogen (premarine), oestriol cream (ovestin). There are several pessaries and vaginal tablets. A soft 5 cm diameter ring Estring-releases oestradiol locally over 3 months and is more user-friendly.

Advantages and disadvantages of vaginal preparations

Advantages- largely active only locally if manufacturers recommendations are followed. Local benefit if systemic treatment is contra indicated.

Disadvantages- expensive, messy, risk of cream being as lubricant..

RISK AND CONTRAINDICATION TO HRT

Risk is considered the denovo development of a potentially serious disease during and in consequence of the administration of HRT. A contra indication is regarded as the exacerbation by HRT of a pre-existing condition.

Endometrial cancer

It has been known for over 20 years that use of oestrogen by itself without progestogen, in a women with a uterus increases the risk of endometrial hyperplasia, [7] cancer. The risk of endometrial hyperstimulation could be almost abolished by the addition of a progestogen and that the protective effect of progestogen depend not only upon daily dose but also upon the duration of administration each month. Maximal protective effect with sequential therapy were observed when the progestogen was added for 12-13 days each month.

Abnormal bleeding with HRT.

The causes and management of abnormal bleeding during HRT have recently been extensively reviewed (Spencer et al 1997). In a summary, two types of abnormal uterine bleeding are recognized with sequential therapies. The first is characterized by heavy or prolonged bleeding at the appropriate time of the cycle. The second type of abnormal bleeding is breakthrough bleeding and this can occur at any time. Tibolone offers a well tolerated therapy which is free from withdrawal bleeding, thus assuring compliance and long term benefits.

Breast cancer

At present, there are no data on the association between breast cancer and use of HRT from randomized controlled trials. Stamfer from Nurses Health Study group has recently stated that use of mammographic services by HRT user in the Nurses Health Study population has been approximately 35-40% greater than use of these services by non-users of HRT. It is tempting to speculate that more frequent breast surveillance of HRT users results in earlier breast cancer detection with a reduced risk of death.

Ovarian cancer

A more recent prospective, cohort study reported no increase in risk with ever use of HRT but observed an increase in risk when use of HRT has continued for 11 years or more.

Gallbladder disease

The largest study to have investigated the association between HRT and risk of gallbladder disease, the Nurses Health Study, reported a 1.5-2.0% increase in risk (Grodstein et al). Furthermore, the risk of cholecystectomy in this study, increased with both oestrogen dose and also with duration of exposure. Non oral route oestrogens may not increase risk because they do not increase bile cholesterol saturation index, biliary salt composition, gallstone formation and after non surgical gallstone therapy, the non oral routes of HRT would be more suitable.

Malignant melanoma

Five studies have reported on the relationship between use of HRT and risk of malignant melanoma. One case controlled study reported a small increase in risk with long term use of HRT, but another case controlled study did not prove it. Thus if HRT increase the risk, than the impact is small.

Venous thrombosis

In November 1996, three studies were published reporting that HRT increased the risk of idiopathic venous thromboembolism. Several studies have shown that oral oestrogen increases coagulation activities but causes other changes that might counteract this effect and the addition of progestogen may also be beneficial.

Transdermal oestrogen, however by avoiding the hepatic first pass effect, does not adversely affect coagulation. However, for a women who has had a VTE or other reasons at increased risk, the transdermal route might be preferable.

Lactose intolerance

People who are sensitive to lactose, may experience variable gastrointestinal and some systemic effects when ingested. Lactose is present as a bulking agent in all the currently available oral oestrogen preparation and all additional oral progestogen except for the progestogen only contraceptive pill Femulen which contains ethynodiol diacetate 500 microgm. This problem is avoided by all the non oral routes of administration.

ADDITIONAL PROGESTOGEN

The need to add progestogen to regimen of HRT for women with a uterus to protect the endometrium is well established and accepted. Many proprietary HRT preparations have contained 10-14 days either separately or combined in the daily tablets. Progestogens are now also incorporated in some matrix patch preparation in either a 28 day sequential regimen, Nuvelle TS and Evorel sequi or a continuous combined regimen, Evorel conti.

Natural progesterone can also be administered via the vagina as a pessary, Cyclogest or a new gel, Cinone. This route avoids the first pass hepatic and intestinal metabolic effects

and causes less side effects than with oral synthetic progestogens. The only proven merit of addition of progestogen is for prevention of endometrial hyperplasia and carcinoma. The levonorgestrel IUCD, Mirena which at present is only licensed in the UK, in combination with oestrogen, administered orally, transdermally or by implant.

CONCLUSION

All routes of administration of HRT are beneficial. For most women the oral route will be simplest, cheapest and most suitable for initial therapy. Thus the average women can now expect to spend approximately one third of her life in a postmenopausal state assuming normal age at menopause. Approximately 9.6 million, some 18% of the total population of the UK sensibly used HRT. HRT will improve the quality of life and prolong quantity. Oestrogen deficiency increases the risk of diseases with a high morbidity and mortality. HRT has been used for prevention and treatment of osteoporosis and also prevent cardiovascular diseases, urogenital atrophy, hot flushes, night sweating, loss of libido, psychological problem, dementia particularly Alzheimer's disease. Future development of intrauterine devices releasing progesterone, vaginal rings and the oral selective oestrogen receptor modulators (SERMS) will further increase the options so that few women will not be able to find some suitable therapy. Selective oestrogen receptor modulators (SERM) exemplified by raloxifene. Members of this family show great potential as non hormonal alternative to existing oestrogen replacement therapy with better risk : benefit ratio and without the requirement for progestogens, nor the anxieties about breast cancer risk. In postmenopausal women, it increases bone mineral density, lowers serum lipids without stimulating endometrium.

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Clipping Anterior Communicating Artery Aneurysm : A case Report

Ehsan Mahmood¹, Asif M. Barkatullah², SIM. Khairun Nabi Khan³, Rezaul Alam⁴

SUMMARY

We are presenting a case who came to us with history of repeated sub-arachnoid hemorrhage (SAH). Carotid Angiogram done in Bahrain reported to show an aneurysm of anterior communicating artery (A com A) aneurysm. Patient was sent back to Dhaka. Patients' condition deteriorated after about 2 weeks. MRI & MRA failed to reveal any clear cut aneurysm. As patient was deteriorating we made a desperate blind approach and found an aneurysm. We clipped the aneurysm. Post operatively patient improved dramatically and after 4 weeks after the surgery patient was neurologically completely stable.

INTRODUCTION

Aneurysm of intracranial arteries are not uncommon. About 51% of all non traumatic sub-arachnoid haemorrhages are due to rupture of aneurysm. There is chance of bleeding in a big number of cases. Different Neurosurgeons have different opinions regarding time of clipping of aneurysm. Carotid Angiogram is still the best method to identify presence of an aneurysm. Recently MRA (Magnetic Resonance Arteriography) is playing a big role in detection of aneurysm. However, successful clipping of aneurysm is the best method of treatment for neurosurgeons as well as patients.

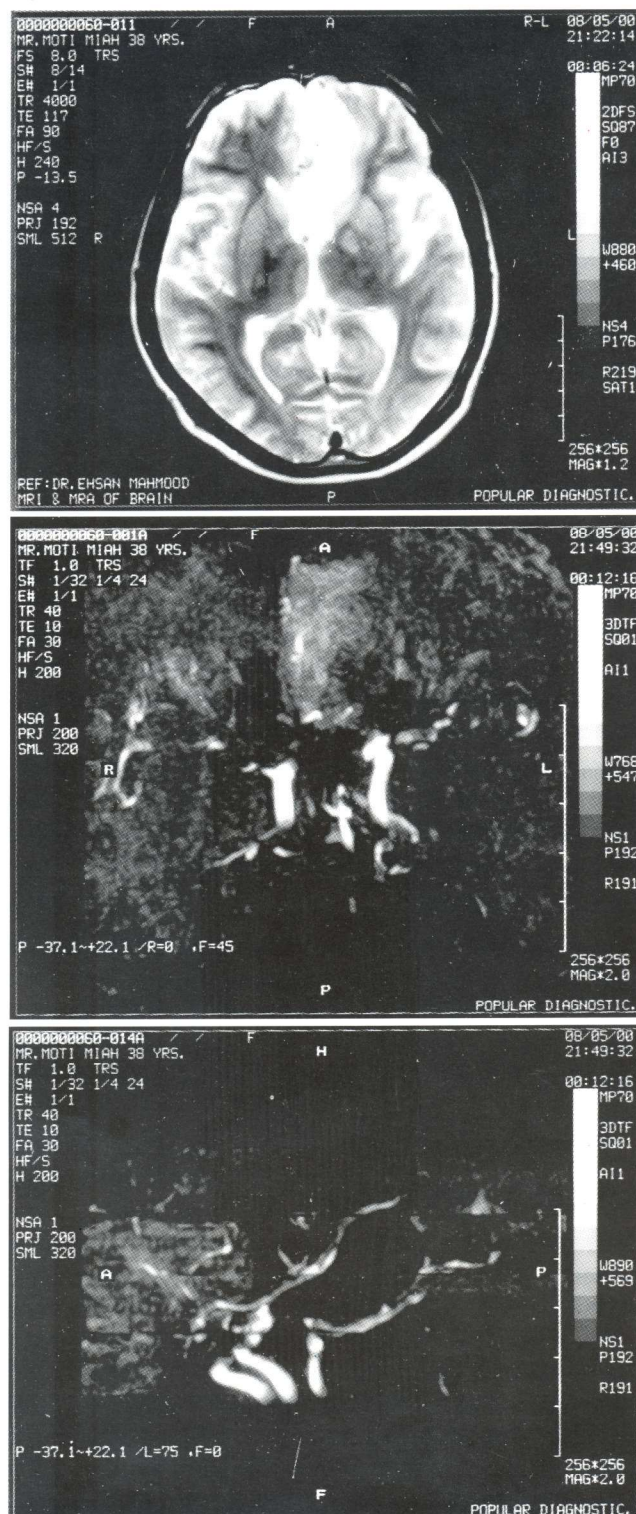
CASE REPORT

A 38 years old right handed Bangladeshi male was admitted in a neurosurgical unit of a Hospital in Bahrain on 22.4.2000 with complaints of acute severe headache of few hours duration followed by loss of consciousness for a brief period. On admission he was fully conscious and had no neurological deficit. Patient was normotensive and had no history of any previous major illness.

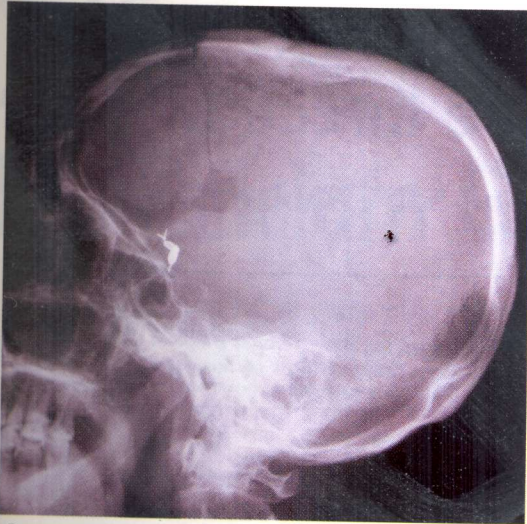
A C.T. scan of Brain was done on 24.4.2000 in Bahrain which showed evidences of SAH. On the following day carotid angiogram was done which showed a left A Com A aneurysm. Patients' condition deteriorated after 10 days. Consciousness level deteriorated and patient developed right sided hemiparesis. As facilities for clipping aneurysm is not present in Bahrain he was sent back to Bangladesh.

On arrival to Bangladesh he was admitted in a clinic in Dhaka. When we examined the patient he was unconscious.

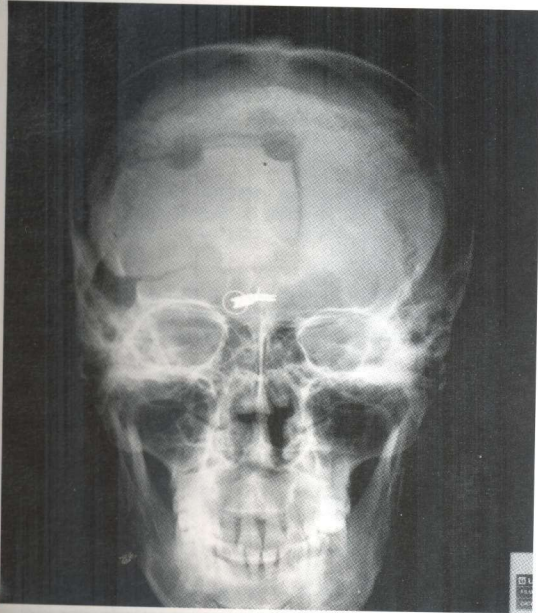
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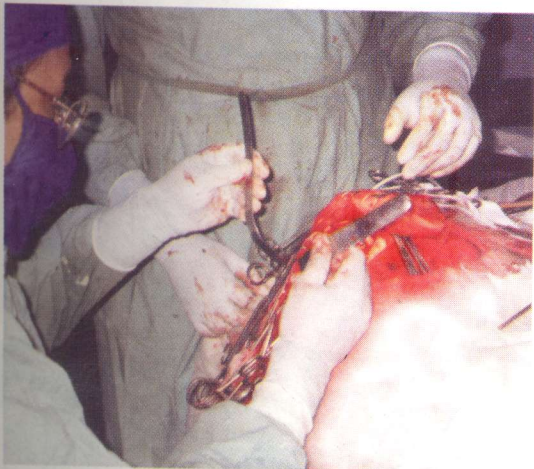
MRI & MRA showing areas where bleeding has occurred. Outline of aneurysmal sac is seen but not very clear.



Post-operative X-Ray skull (lateral view) showing position of clip.



Post-operative X-Ray skull (A/P view) showing position of clip.



Prof. Ehsan Mahmood performing the operation: Clipping Anterior Communicating Artery Aneurysm.

Patient had right sided hemiparesis of grade 2/5. We tried to improve the condition of patient with conservative treatment but condition was deteriorating. MRA was done but it couldn't give us clear picture of position and site of aneurysm due to presence of blood clots. So we decided to explore and clip the aneurysm.

On 11.5.2000 after pre-operative preparation, left frontal craniotomy was done. Left frontal lobe was retracted upward. Evidences of old haemorrhage and blood clot was found. Left olfactory nerve was sectioned. Gyri Recti was dissected and the fundus of aneurysm was found lying over the optic chiasma. It was dissected and separated from surrounding tissue. During the process of dissection, fundus ruptured. The bleeding was controlled and self retaining aneurysm clip was applied to neck of aneurysm. Wound was then closed in layer as usual.

Patient received Nimodipine 60mg 4 hourly post operatively for 3 days along with other medicines. After 3 days Nimodipine was tapered slowly.

Post operative recovery was excellent. Patient was fully conscious on 7th post-operative day. Patient was discharged on 10th post-operative day with advice to continue anticonvulsant and physiotherapy. His right-sided weakness improved rapidly and 4 weeks after surgery, patient was neurologically completely stable & his muscle power was 5/5.

DISCUSSION

Once it was thought that incidence of SAH are less in South Asia. But Ramamurthi and Tandon proved that incidence of SAH are almost same in South Asia as compared with Europe and America. Most of them remain undiagnosed and a vast number of patients die due to rebleeding or other complications.

Of all SAH, rupture from aneurysm accounts for 51% of cases. Diagnosis is done by direct carotid angiography or transfemoral 4 vessel angiography. Recent advances are digital subtraction angiography and more recently Magnetic Resonance Arteriography (MRA).

The Principle of treatment is to separate this aneurysm from circulation without hampering normal circulation of brain. This is achieved by clipping the neck of aneurysm, putting suture in neck of aneurysm, excision of sac and microsuture, provoking thrombosis of aneurysm, wrapping aneurysm with cottons to induce fibrosis etc. However the treatment of choice is still clipping the neck of aneurysm.

Our patient worsened after rebleeding which is often fatal. We had no other choice but to find out the aneurysm. We were fortunate to find the sac of aneurysm and able to apply clip in the neck of it. Carotid angiogram or MRA done at proper time to find out aneurysm of anterior or posterior circulation of brain and clipping the neck of aneurysm will definitely help a lot of patients with SAH after aneurysmal rupture.

ACKNOWLEDGEMENT

We like to thank Dr. Golam Mohiuddin, Sr. Consultant Neurosurgeon, Holy Family Red Crescent Hospital who has kindly supplied us Aneurysm clip and applicator.

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Efficacy Study of Maprocin and Nidazyl in Management of Post-operative Infection

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ABSTRACT

Background : Surgical Site Infections (SSIs) are the most common nosocomial infection, accounting for 38% of all such infections. Two third were confined to the incision and one third involved organs or spaces accessed during the operation. SSIs remain a substantial cause of morbidity and mortality among hospitalized patients and an appropriate antibiotic regimes of Ciprofloxacin and Metronidazole may be effective to prevent it.

Aim : To identify factors related to Surgical Site Infection to operative patients which can be reduced or eliminated by Maprocin (Ciprofloxacin) and Nidazyl (Metronidazole).

Method : One hundred and twenty patients of different surgical cases were administered Inj. Maprocin and Inj. Nidazyl in both per and post operative period for two days which was followed by Tab. Maprocin & Tab. Nidazyl for three days. Doses were also regulated according to the requirement on case basis. Efficacy was noted by observing wound healing, absence of pain & pyrexia and side-effect of the drugs concerned.

Results : Among 120 patients, 56 cases were Chronic Cholecystitis with Cholelithiasis, 06 cases Inguinal Hernia, 05 cases Multinodular Goitre, 04 cases Gastric Outlet Obstruction and different other surgical cases. The overall SSI rate was 01.66% which was due to ciprofloxacin resistance and complications of malignancy. The success rate of the efficacy study of Maprocin and Nidazyl is 98.34%.

Conclusion : The results followed by the trial scientifically proves the efficacy of Maprocin and Nidazyl in both parenteral and oral forms. The study report also shows the excellent success rate of Maprocin and Nidazyl in antimicrobial prophylaxis and highly effective in management of post-operative infection.

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বঙ্গবন্ধু শেখ মুজিব মেডিক্যাল বিশ্ববিদ্যালয়
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June 29, 2000.

EFFICACY STUDY OF MAPROCIN AND NIDAZYL

A study was conducted on 120 patients in Surgery unit I-A, Bangabandhu Sheikh Mujib Medical University (BSMMU), under direct supervision of the undersigned to evaluate the efficacy of Maprocin (Ciprofloxacin) and Nidazyl (Metronidazole), both parenteral and oral forms, manufactured by Orion Infusion Ltd. and Orion Laboratories Ltd. respectively. The trial has been conducted in routine surgical procedures mainly.

The result showed excellent success rate for this combination antibiotics, Maprocin and Nidazyl which is 98.34% and only two patients developed wound infection who were resistant to Ciprofloxacin.

The above findings indicate that Maprocin and Nidazyl are highly effective in the prevention of post-operative infection as a sort of prophylactic antibiotic regimen as far as this random study is concerned.

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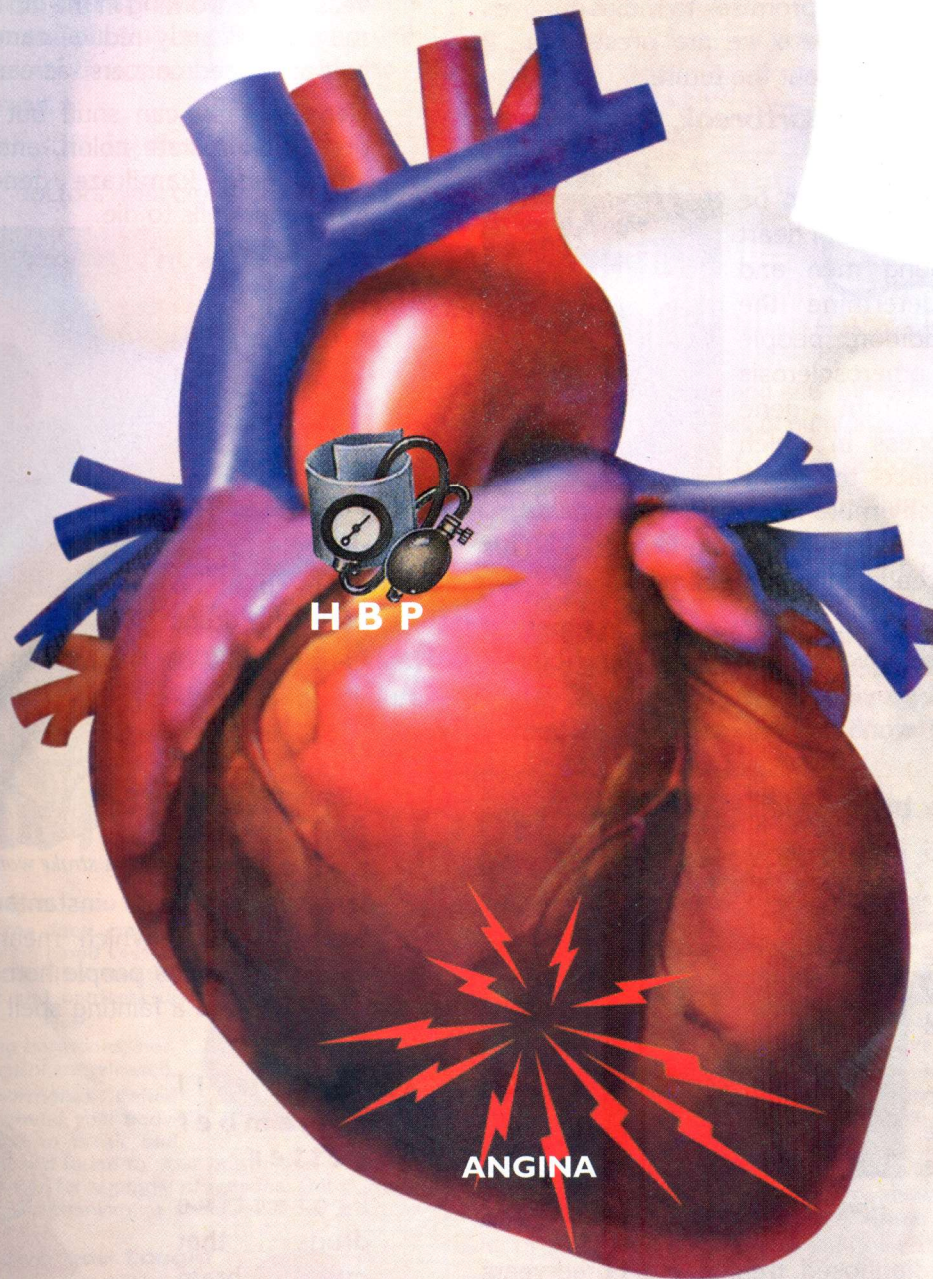
ম্যানেজমেন্ট অব পোস্ট অপারেটিভ ইনফেকশন সিথোফ্লক্সাসিন ও ম্যাট্রোনিডাজল-এর ভূমিকা শীর্ষক সেমিনার শেষে ওরিয়ন মেডিক্যাল সার্ভিসেস জিপার্টমেন্টের ব্যবস্থাপক ডাঃ আজিজুর রহমানের হাতে সনদপত্র প্রদান করেন বঙ্গবন্ধু মেডিক্যাল বিশ্ববিদ্যালয়ের সার্জারি বিভাগের চেয়ারম্যান অধ্যাপক আতা-ই-রাব্বী

সিথোফ্লক্সাসিন ও ম্যাট্রোনিডাজল' ওষুধের জন্যে এফিকেসী ট্রায়াল সনদ পেলো ওরিয়ন

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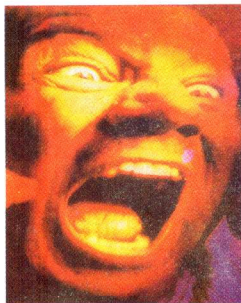
Future Medicine

Astonishing Medical Predictions for the Next 25 Years

We live in the 21st century, and though the world may be getting crowded, science promises to make our lives easier, our health better. Here we are presenting 9 reasons to stop worrying about the future.

1. You may die of heartbreak, but not of heart disease.

By 2010, doctors hope to be able to spot faint signs of heart disease in young men and women, to determine the disease. In addition, people with chronic atherosclerosis may benefit from gene therapy, a process in which physicians replace the gene that makes a body more likely to accumulate artery-clogging plaque. This procedure is already successful in mice.

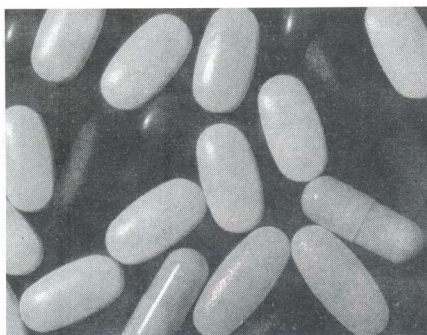


Die of heartbreak!

Within 25 years, we may also have outpatient surgeries that remove arterial plaque, and cloned animals could provide a steady supply of valves and heart that won't be rejected by the human body.

2. Cancer won't be a killer.

Within 15 years, researchers hope to be using extremely sensitive tests of blood, urine, and saliva to detect the slightest traces of cancer proteins. Many cancers will be diagnosed, treated, and cured years earlier than they are now.



Drugs will stop cancer within 15 years

Vaccines for liver cancer, lymphomas, melanoma, and even prostate cancer may be developed within two decades.

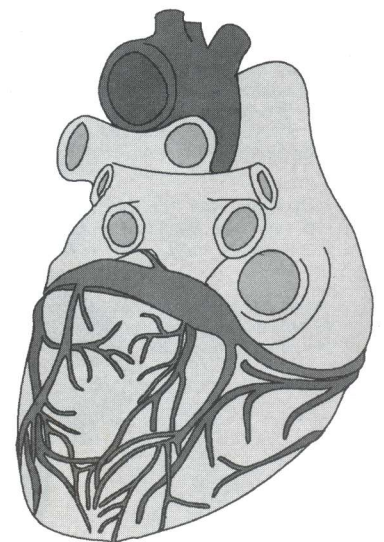
By 2015, physicians will use drugs that block only the particular molecules that allow certain cancer cells to grow.

Drugs that stop cancer from forming new blood vessels are working in the lab right now. Such drugs may significantly reduce cancer deaths- and even halt advanced cancers -as early as 2010.

Gene therapy can snuff out the cancer- causing genes in prostate colon, and pancreatic cells by introducing kamikaze genes that direct the malignant cells to die.

3. A stroke won't render you helpless.

By 2020, doctors will be able to put patients in hyperbaric oxygen cooling chambers and administer neuro protective drugs that preserve brain tissue before irreversible damage occurs, and also guide precisely targeted drugs to instantaneously unclog the blocked artery. Which means the life changing ordeal that sends people home in wheelchairs may be reduced to a fainting spell followed by four or 5 sick days.

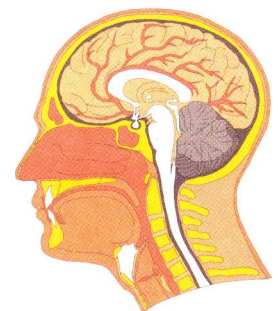


A stroke won't render you helpless.

4. You will remember better.

Protective drugs that guard brain tissue against Alzheimer's could be available in 15 years, and

soon thereafter physicians may be able to correct the damage done by the Alzheimer's gene.



You will remember better.

5. Diabetes will be easily manageable .

First researchers hope to introduce insulin pills and inhalers within a few years. An even more radical development: Within 25 years, physicians may routinely use gene therapy to regenerate the insulin- producing pancreatic cells or force other cells to produce insulin. Pancreatic cell transplants (much safer than substituting a new organ) with bio-engineered animal tissue are also coming as is an artificial pancreas.

6. You'll never feel stiff in the morning.

Within 20 years, doctors will clone the cells that



You will never feel stiff in the morning.

produce healthy cartilage (called chondrocytes) and transplant them into joints. This procedure could render most arthritis sufferers pain free.

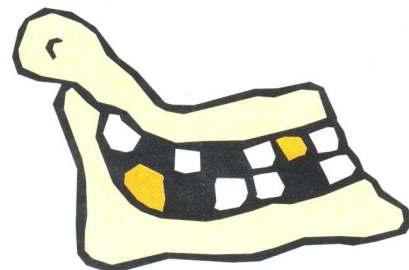
7. You will never lose your hearing.

By 2020, researchers hope to have gene therapy that will regenerate cochlear- hair cells in humans. This will reverse most age-related hearing loss.

8. You will be able to take your teeth to your grave.

Within 15 years, dentists will fuse tooth enamel crystals with lasers to make them impervious to decay producing acids from bacteria.

And mouth washes spiked with antibacterial and anti- inflammatory agents will tame even extreme cases of gum disease.



You will be able to take your teeth to your grave.

9. You will rise to the occasion without fail.

Within a few years, doctors hope to have drugs that promote regular night time erections to keep the penis oxygenated and healthy. And by 2020 men will take daily drug to prevent the gradual buildup of penile scar tissue. For severe situations, they will use gene therapy to regrow damaged penile muscle. Men who need only an occasional boost will be able to choose from a variety of easy-to-use oral drugs and medicated gels.

What Happens???

What Happens when you Smile?

- * The muscles of the face crease, massaging underlying blood vessels and stimulating blood flow and the supply of oxygen and nutrients to the brain.
- * The stress relieving hormones, nor-adrenaline and cortisol are released.
- * Those happy hormones called endorphins, whiz around your body. Have you ever had to break bad news to somebody and found to your horror that you can't help smiling? We smile for a gaggle of reasons. But primarily it is a bonding mechanism, a social skill we learn as babies.



What Happens when you Laugh?

- * The heart beats quicker, boosting circulation.
- * The skeletal muscles get a minor work out, stimulating nerves.
- * The body takes in more oxygen.
- * Stale air is expelled from the lungs.



What Happens when you CRY?

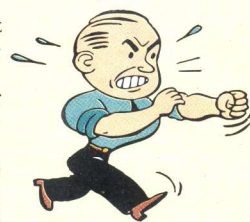
- * The eye secretes 50 to 100 times its normal amount of fluids.

- * Tears are produced by the lachrymal glands, triggered into a squeezing action by any stimulation from a piece of fluff that flies into the eye to the sight of something that hurts you emotionally. The muscles squeeze out the liquid from your eyes.
- * Body temperature rises, the heart beat goes up, lungs and respiratory muscles pound. adrenaline.
- * Breathing deepens, the heart beats more rapidly, blood pressure rises, and pupils dilate.
- * Blood is diverted from other organs to the heart, central nervous system, and muscles.



What Happens when you're Angry?

- * The brain tells the body to pump out the action- hormone nor-adrenaline.
- * Breathing deepens, the heart beats more rapidly, blood pressure rises, and pupils dilate.
- * Blood is diverted from other organs to the heart, central nervous system, and muscles.
- * Digestion is suspended, glucose levels rise, men have a testosterone boost. You're on red alert.



Medi Tips

PRACTICE TIPS

Microwave medicine

The application of moist heat is often prescribed to accelerate suppurative processes (such as superficial abscesses) and to reduce pain, oedema, and spasm in inflamed or injured muscles, tendons, and joints.

An alternative to the professional packs used by physical therapists is the use of moist towels heated in a microwave oven. A small, thin towel is moistened, placed in the oven, and heated for 20 to 30 seconds. *The temperature of the towel must be checked to avoid burning the patient.* The heated towel is then wrapped in a dry towel of the same size and applied to the affected area for 20 minutes. This may be repeated four or five times a day.

Finding the right vein

Drawing blood from a patient who is obese or who has had frequent phlebotomy procedures can be difficult because palpable superficial arm veins are not apparent. Rather than attempting a blind stick or resorting to an alternative site, find the brachial artery pulse in the antecubital space. Lying immediately medial and lateral to the brachial artery are the paired brachial veins. It is easy to obtain venous blood from the adjacent brachial vein by palpating the brachial artery as a landmark and inserting a standard phlebotomy needle just lateral to it.

Distract and conquer

Small children (about 18 months to 5 years old) have a difficult time understanding how to breathe in and out on command during a chest examination and sometimes may downright refuse. It is found that asking them to try to blow out physician's penlight while listening to their chest for adventitious sounds is a successful way of eliciting the necessary behavior.

A reminder to be warm

To avoid placing a frigid stethoscope on a patient's back, try warming your stethoscope by rubbing the diaphragm briskly in the palm of your hand. The friction takes the chill off the instrument, and patients appreciate the difference. This also helps keep babies from startling and crying during an examination.

Stethoscope hearing aid

Conducting an interview with a hearing-impaired patient may be difficult to do without shouting. One simple solution is to place the earpieces of a stethoscope on the patient's ears and speak into the diaphragm. This often amplifies the physician's voice enough to allow effective communication.

Oral antibiotic for conjunctivitis

"Resistant" cases of conjunctivitis in children often occur because the parents are unable to carry through on therapy with antibiotic eyedrops. Very young children in particular seldom give parents a chance to instill drops the second time around. It is better to prescribe an oral antibiotic (usually a tasty form of amoxicillin) for all cases of suspected bacterial conjunctivitis in children younger than 8 years old. You will find quick responses, happy patients and parents, and no treatment "failures" from noncompliance.

Abscess technique

When you incise and drain an abscess, excise a small elliptical piece of skin at the drainage point. This has the following advantages:

1. Allows continued drainage of the abscess.
2. Eliminates the need for sterile packing or catheters to keep the abscess draining.
3. Is more comfortable for patients than other techniques.

Medi News

From Internet/Journal

Zinc - A medicine for the 21st century

"It is entirely possible that future progress in molecular biology may elucidate the basic mechanisms and causes of most diseases. It seems likely that the next century's treatments will implement natural body chemicals that restore the patient to a normal condition, rather than drugs that result in an abnormal condition. The world may eventually learn the wisdom of **Pfeiffers Law** (Dr Carl C. Pfeiffer): For every drug that benefits a patient, there is a natural substance that can achieve that same effect." So writes Dr William Walsh of the Carl Pfeiffer Treatment Center in Naperville (ilinois), USA. Dr Walsh researches the relationship between zinc deficiency, metal metabolism and behavior disorders. He says, "research has shown zinc to be far more important than previously believed and low levels of zinc are associated with behavior disorders. We find that zinc deficient individuals usually respond well to inexpensive supplementation with zinc and augmenting nutrients. Many patients who previously experienced years of counseling, psychotherapy, aggressive medication programs, and/or residential treatment become greatly improved and respond to less intensive (and less expensive) therapies. Zinc deficiency can be corrected, but not cured. If treatment is discontinued, the prior zinc deficiency will reemerge with all symptoms gradually returning. Zinc deficiency, like diabetes, requires life long treatment. Fortunately, It is simple, low cost, safe treatment".

www.zincworld.org

Calls made for improvements in Bangladeshis' physical health

Despite Bangladesh's recent gains in reducing fertility rates and improving general health, more than 60% of its 124-million population still has no access to modern health-care services, according to "Quest for a Healthy Bangladesh", a report released by the World bank. "Less than 40% of the population has access to modern primary health services beyond immunisation and family planning; only 25% of pregnant women receive antenatal care; and the country's maternal mortality rate of 4.5 deaths per 1000 is one of the highest in the world", said author Henry Perry.

Bangladesh, the report noted, is one of the few countries in the world where women have a shorter life expectancy than men, mainly because women are discriminated against in the provision of food and health care.

In addition, rates of malnutrition in the country are among the highest in the world; more than a third of the 3.33 millions infants born each year are underweight, and 60% of children (aged 6-17 months) are either stunted or wasted.

Although the country has significantly reduced its birth rate, its population is expected to double by 2035-even if a replacement rate of 2.2 births per women is achieved by

2005. The report highlighted "New threats", including accidents, HIV and tuberculosis, arsenic, and tobacco that have so far received limited attention. Accidents and injuries, it noted, kills 17000 people each year, a rate 23 times greater than that of most European countries. According to the report, almost 50% of men in Bangladesh smoke at least an occasional cigarette daily, and the long-term effects of arsenic poisoning, to which one third of the population may be exposed, may include a substantial increase in the burden of cancer.

The report recommended systemic changes in the Ministry of health and Family Welfare to promote accountability to the community, improve productivity of health-care staff,



Healthy Bangladesh—Long way to go.

encourage decentralisation, improve quality of care, and increase the involvement of donors and non-governmental organisations.

THE LANCET. VOL-355 MARCH 11.2000.

Vitamin C For Blood Pressure?

If you have moderately high blood pressure all you probably need is extra Vitamin C (rather than anti-hypertensives) to reduce your levels. A study reported in the Lancet revealed that it took Just 500 milligrams of vitamin C to drop systolic pressure by about 13 points and diastolic pressure decreased by 8 points, reductions similar to those seen with anti-hypertensive medication. As vitamin C is incredibly easy to get in fruits and veggies (go for amla, guava, berries, mosambi, mango, green leafy veggies, peas, cabbage and french beans) It may be a good alternative to anti-hypertensives.

www.bmj.com

Vitamin C and gallstones

Low serum ascorbic acid concentration may be a risk factor for gallstone formation in women, says Joel Simon (University of California, San Francisco, CA, USA), who found the connection by analysing data from



Vitamin C For Blood Pressure? Vitamin C to reduce gallstones!

7042 women, and 6086 men enrolled in the US Third National Health and Nutrition Survey. An increase (0.5 mg/dL or 27 mmol/L) in ascorbic acid concentrations was associated with a 13% lower prevalence of clinical gallbladder disease and symptom-free gallstones (*Arch Intern Med* 2000;160:931-36). "Vitamin C doses between 250 and 500 mg would be more than adequate [to achieve the potential risk reduction] and are probably obtainable by diet alone", says Simon. The study is suggestive, but not definitive", comments Robert Jacob of the US Department of Agriculture.

THE LANCET . Vol 355. April 22, 2000

Smoking in parents increases meningococcal disease risk

The risk of invasive meningococcal disease in children is strongly influenced by parental smoking and unfavorable socioeconomic circumstance, according to new research.

The largest increase in risk-more than eightfold-was among children of parents who both smoked, although researchers warned this may be an over estimate, because such families are likely to have multiple social disadvantage not covered by the study's adjustment for those factors.

The research found that children in households where 20 cigarettes a day were smoked were 2.6 times more likely to develop meningococcal disease than children in the control group.

The study, published in the *Archives of Disease in Childhood* (2000;83:117-2) examined all the cases of invasive meningococcal disease diagnosed over 18 months in 35 districts of the Czech Republic. A total of 71 cases were identified in children under 15 Years.

To each case, two controls were matched by age, sex, district, and place of origin (urban or rural). The controls were recruited from healthy children at the same schools as the cases. The authors said that the

proportion of smoking parents was substantially higher among cases than controls. They identified several socio-economic factors, notably maternal education, as being important in determining risk of the disease. The report also points to a number of biological possibilities put forward for a link between smoking and meningococcal disease.

The authors stated "Exposure to smoke causes direct damage to the nasopharyngeal mucosa. Passive smoking is associated with increased risk of respiratory disease in young children".

www.bmj.com

Report bodes ill for antioxidant supplementation

Insufficient evidence exists to support claims that taking megadoses of vitamins C and E, carotenoids, or other antioxidants can prevent chronic disease, according to a report on Dietary Reference Intakes (DRI) released by the US Institute of Medicine. The report, a collaboration between the USA and Canada, also sets upper limits on daily consumption of these nutrients to reduce the risk of adverse side-effects. "We have this big reservoir of population studies that suggest links between antioxidants and chronic disease, but don't define them to the point where you can take them to the bank and use them as recommendations", says DRI committee member Robert Jacob of the US Department Of Agriculture. "When we eat foods, We get a number of antioxidants, and it's very likely that no single one is the magic key to preventing oxidative damage and reducing chronic disease risk", he asserts. "The very few clinical trials of vitamin C have had mixed results up until now. Until we see a lot more positive results, many scientists will remain skeptical".

The report recommends an increase in daily vitamin C



Too much of good thing?

intake to 75 mg for women and 90mg for men, to achieve maximum saturation in the body. Smokers require an extra 35 mg daily because of greater exposure to oxidative damage. The upper daily intake level is 2g, to avoid diarrhoea. Recommended Vitamin E

daily intake from food is increased to 15 mg for both women and men. The equivalent from supplements is 22 IU of d-alpha-tocopherol ("natural" source) or 33 IUs of dl-alpha-tocopherol ("synthetic" form). The upper limit is 1 g of alpha-tocopherol (about 1500 IU of natural vitamin E or 1100 IU of the synthetic form). Selenium intake of 55µg daily recommended, with an upper intake level of 400µg. No recommended intakes of β-carotene or other carotenoids are suggested because of contradictory risk-benefit data.

β-Carotene supplementation is recommended only for prevention and control of vitamin A deficiency. People should "use caution" before taking them in higher doses, The report warns.

THE LANCET . Vol 355. April 22, 2000

High-fibre diet improves type 2 diabetes control

For patients with late-onset diabetes, a diet rich in natural high fibre foods offers better glycaemic control than the diet recommended by the American Diabetes Association (ADA), according to a new study. In the ADA diet, saturated fat is replaced with monounsaturated fat, since this approach is thought to be the basis for the healthy effects of Mediterranean diets.

However, a little-emphasised aspect of such diets is their high natural fibre content. Manisha Chandalia (Texas University Southwestern Medical Centre, TX, USA) and colleagues aimed to find out whether glycaemic control could be improved simply by increasing the natural fibre content of the diet.

13 patients (mean age 61 years) with type 2 diabetes were randomly assigned the ADA diet (containing, 24g fibre/day) or a high fibre diet (50g fibre/day) for 6 weeks. Next, patients followed an isocaloric diet for 7 days, then switched to the alternative diet for 6 more weeks. Only unfortified foods high in soluble fibre-eg, raisins, zucchini, oats, and granola were included (*N Eng J Med* 2000; 342:1392-98).

When patients followed the high fibre diet, mean daily glucose concentrations were 0.7 mmol/L lower ($p=0.04$), and mean daily urinary glucose excretion was 1.3 g lower ($p=0.008$) than when patients followed the ADA diet. The high-fibre diet was also associated with decreases in 24-h plasma glucose and insulin concentrations, plasma total cholesterol, triglycerides, VLDL and gastrointestinal absorption of cholesterol.

"Except for sample size, the study design is impeccable", says Gerald Watts (Royal Perth Hospital and University of Western Australia), "but I wonder how practicable this diet is going to be: 50g a day is a lot. "Most found it "palatable" says Chandalia, and they liked the regular bowel habit. Recent reports questioning the protective role of fibre in disease should not dissuade physicians from actively promoting natural high-fibre diets to diabetic patients, she concludes.

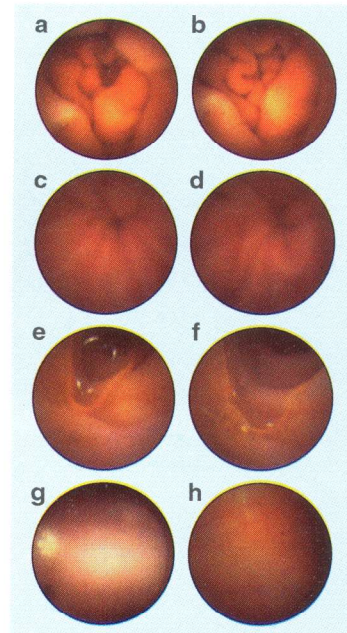
THE LANCET . Vol 355. May 20, 2000

Wireless Capsule Endoscopy

Unpleasant endoscopic procedures to visualise the small bowel may be a thing of the past, according to a recent report. The investigators describe how a swallowable capsule containing a small camera can transmit pictures using UHF-band radio-telemetry to aerials taped to the patient's body. According to the authors, high quality images can be received throughout the video transmission, which can last for up to 6 hours.

NATURE/ VOL /MAY 2000

Samples of images of the small bowel acquired by the capsule endoscope of human in vivo studies. a,b, Gastric folds in the body of the stomach; c,d, villous pattern of the small bowel enhanced by the presence of a little water and an air bubble in the lumen; e,f, airless images of normal jejunum, viewed with the lumen closed in front of the optical dome of the capsule; g,h, views of the terminal ileum.



Weak in the knees

People who overweight as young adults appear to be especially vulnerable to knee problems as they get older, according to a study published in the December 1999 issue of *American Journal of Medicine*.

John's Hopkins researchers followed 1,180 people aged 20 to 29 for an average of 36 years. They found that subjects who were heaviest at the start of the study (body-mass index greater than 24.7) were three times more likely to have arthritis of the knees by age 65 than those who had BMIs of less than 22.8. A higher BMI during young adulthood did not increase the subjects' risk for hip arthritis, suggesting that knee joints bear the brunt of damage from excess weight. So stay slim when you're young to prevent problems later.

www.bbc/health.com

Brittle Bones, Brittle Brain?

A new study from the University of California, San Francisco, shows a link between osteoporosis and decreased brain function. Researchers who studied more than 8,000 older women found that those with low bone-mineral density scored lower than average on cognitive tests. Play it safe by watching your calcium intake now-and your estrogen levels later, since they both play a role in bone density.

www.bbc/health.com

Information for Authors

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The text of clinical articles should not exceed 1,000 words (for double-spaced pages). Suggested order of presentation is cover page, text, summary reference list, tables, figure legends, author affiliation (s).

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On the cover page, indicate the article title and designate a corresponding author, for each author, list full name, highest pertinent academic degree, title of current position, address, office phone and fax numbers. For the corresponding author, provide this information plus e-mail address and home phone number.

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2. Boucher RC. Cystic fibrosis, In Isselbacher KJ, Braunwald E, Wilson JD, et al, eds, *Harrison's principles of internal medicine*. 13th ed New York : McGraw-Hill, 1994 : 1194-7

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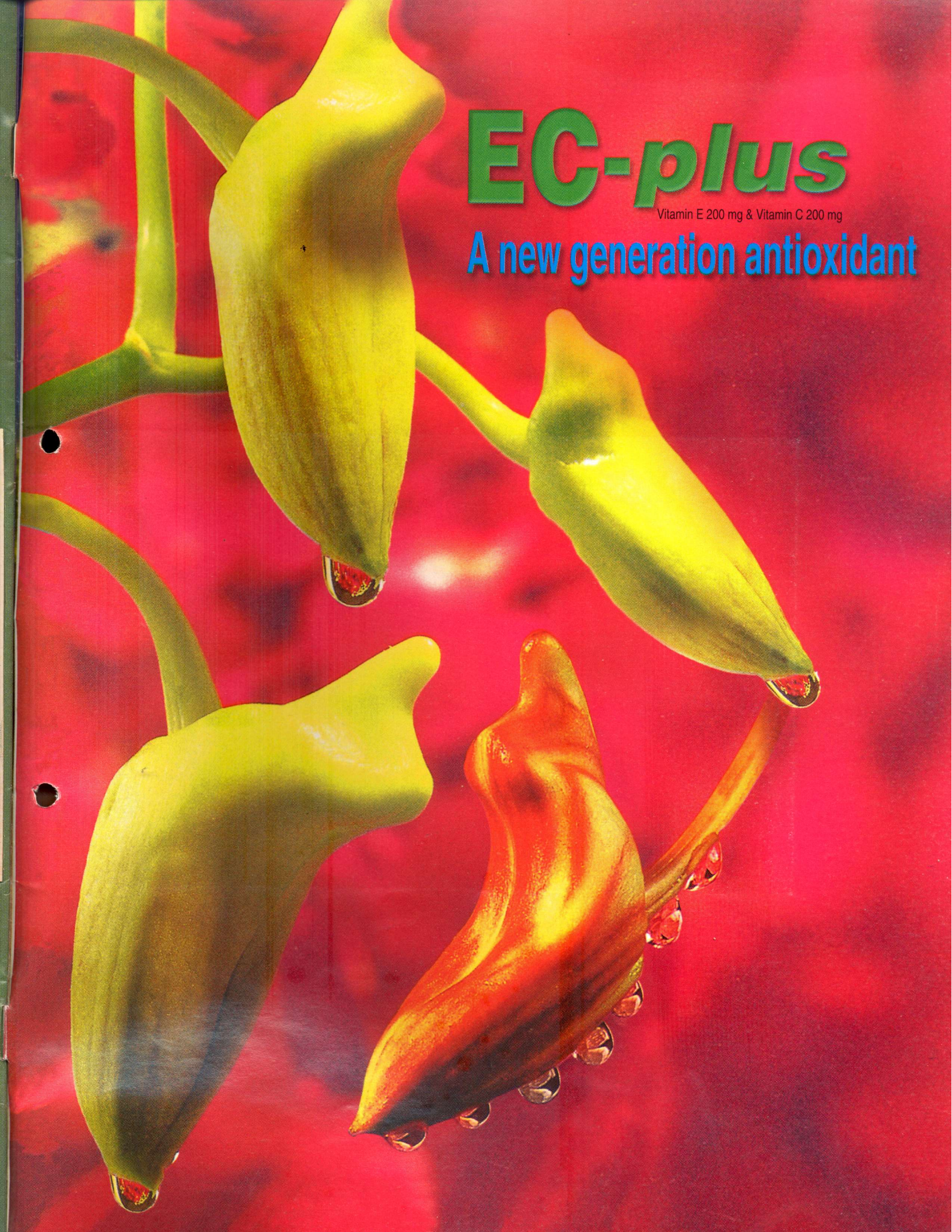
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The background of the advertisement is a vibrant, textured red. Four bell peppers are arranged diagonally from the top left to the bottom right. Three of the peppers are a bright, glossy green, while the one at the bottom right is a rich, glossy red. Each pepper is covered in numerous clear water droplets of varying sizes, giving it a fresh, dewy appearance. The lighting is soft, highlighting the smooth texture of the peppers' skin.

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