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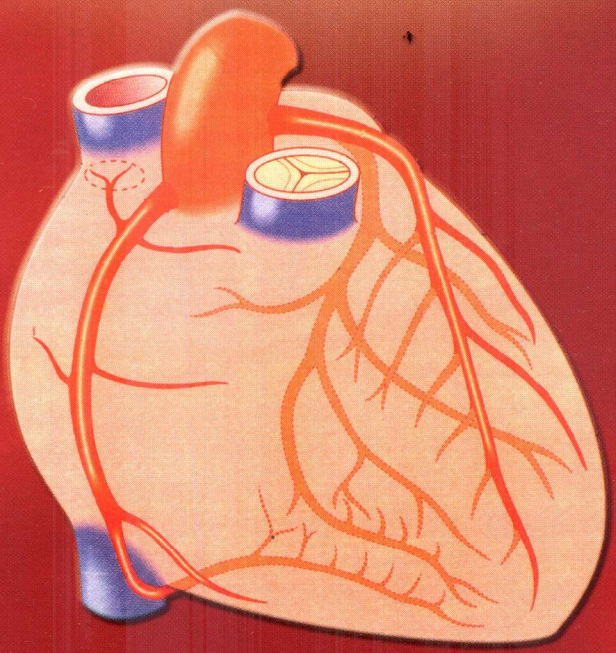
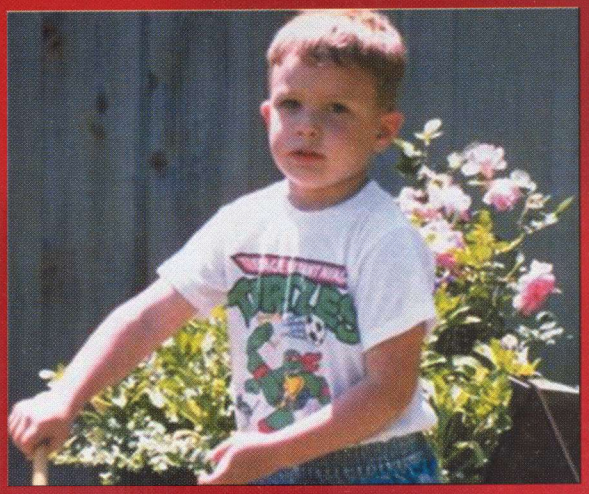


Acute Coronary Syndrome : Management of the patients with Unstable Angina and Non-ST Segment Elevation Myocardial Infarction



Hemophilia in pediatric surgery : A study in a Hospital, Bangladesh

Viral Bronchiolitis : An update on a recent epidemic

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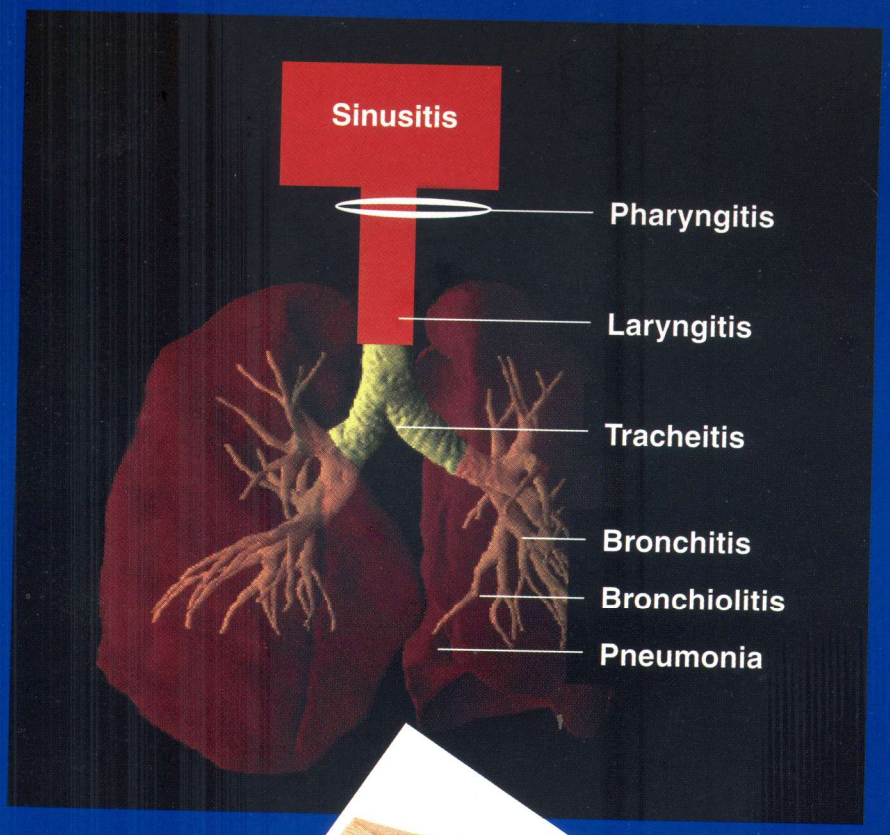

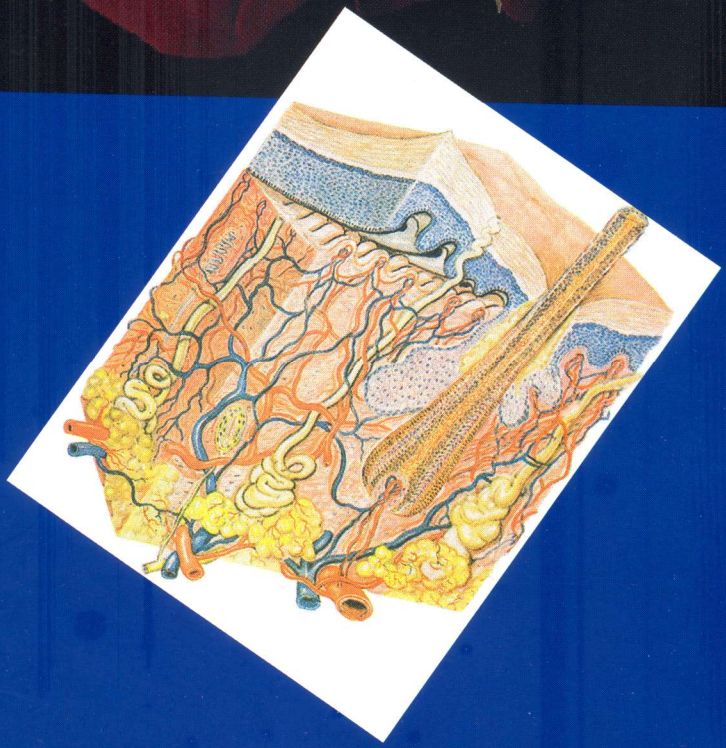

Decisive against RTI and Skin & Soft Tissue Infections

The ORION Medical Journal

Contents

COVER ILLUSTRATION

Pictorial depiction of Acute Coronary Syndrome by diagram of heart with complete coronary circulation, Hemophilia in pediatric surgery by the picture of a child looks apparently healthy but hemophilic, was not detected by blood examination (BT, CT) before circumcision, Viral Bronchiolitis by the picture of relaxed mood of a mother with an improved child suffered from bronchiolitis.

PUBLISHER'S NOTE

We acknowledge to quote different authors regarding their original contributions in the text books, journals and manuals etc. We reiterate that these deliberations are not of commercial uses and values. The views expressed in this publication do not necessarily reflect those of its editors or of Orion Laboratories Ltd.

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Editorial

Our mission and vision is to care and cater latest medical information of academic interest to the professionals and to remain active participant in Continued Medical Education program. This scenario has turned into reality through your suggestions, inspirations and patronizations

In this era of modern information technology it is our privilege and pleasure in recent hosting our web site www\\orion-group.net to keep regular contact with our patrons at home and abroad. Our journals are available on line. You may please contact with us through journals@orion-group.net.

We believe that "The Orion" is gaining widespread confidence of the professionals in disseminating and updating the knowledge of medical science by guidance of honorable members of the Advisory and Review Board and also well experienced Consultant Editor and Guest Editor.

This is our 12th publication and we have focused Ischemic Heart Diseases by "Acute Coronary Syndrome: Management of the Patients with Unstable Angina and Non-ST Segment Elevation Myocardial Infarction", Pediatric Surgery by "Hemophilia in Pediatric Surgery : A Study in a Hospital, Bangladesh", Bronchiolitis by "Viral Bronchiolitis : An update on a recent epidemic".

World population is facing a great problem to combat Cardiovascular Diseases-mostly Ischemic Heart Diseases. Of these Ischemic Heart Diseases, Acute Coronary Syndrome disables a large number of people in their productive and active years and kills them . Researchs and trials are going on to find the most effective ways of treatment minimizing complications .

Hemophilia, Sex-linked recessive bleeding disorder, mostly is detected by pediatric surgeons during circumcision. There is no statistical data of hemophilic patients in our country. People also are not well aware of this disease. Sometimes hemorrhage could not be stopped by usual procedure. Circumcision in this respect is blessing as it helps in detecting this devastating problem in early life with subsequent effective management of hemophilia reducing morbidity and mortality. Comprehensive treatment centers for hemophilia should have a close association of surgeons, hematologists, pediatricians and blood bank personnel with adequate facilities and appropriate supports.

Among pediatric medical problems Bronchiolitis is the most significant respiratory illness of infants and young children. Its incidence is as high as 11 cases per 1000 per year of both first and second six months of life in our country. Prematurity, PEM, artificial feeding, crowded environment and exposure to smoking are the risk factors for bronchiolitis in infancy. Preventive measure is a major part in the management and treatment of bronchiolitis and needs supports from public sectors.

We always value your views, ideas and suggestions to enrich the publication.

May The Almighty bless you in the spirit of good health and professional achievement.

Dr. ATM Azizur Rahman
Chief Editor
and
Manager,
Medical Services Department.

Acute Coronary Syndrome : Management of the patients with Unstable Angina and Non-ST Segment Elevation Myocardial Infarction

Sufia Rahman[1], Kazi Atiqur Rahman[2]

Introduction

Acute Coronary Syndrome (ACS) kills and disables people in their most productive years. Rupture atherosclerotic plaque leading to thrombus formation in a coronary artery is the basic mechanism of ACS. Ischaemic syndrome [Unstable Angina (UA), Non-ST segment elevation myocardial Infarction (NSTEMI) and ST-Elevation myocardial Infarction] represent a continuum that has come to a common term ACS.

Definition of Acute Coronary Syndrome

Acute coronary syndrome refers to any constellation of clinical symptoms that may indicate acute myocardial Infarction.

Recent guideline published by American College of Cardiology (ACC) and American Heart Association (AHA) gives more emphasis on the management of patients with Unstable Angina and NSTEMI, two very important component of ACS.

UA and NSTEMI are acute coronary syndroms (ACSs) that are characterized by an imbalance between myocardial oxygen supply and demand. UA and NSTEMI are considered to be closely related conditions whose pathogenesis and clinical presentation are similar but of differing severity. They differ primarily in whether the ischaemia is severe enough to cause sufficient myocardial damage to release detectable quantities of marker of myocardial injury, most commonly troponin I ((Tn I), troponin T (TnT) or CKMB[1].

Once it has been established that no biochemical marker of myocardial necrosis has been released (with a reference limit of 99th percentile of the normal population), the patient with ACS may be considered to have experienced UA, whereas the diagnosis of NSTEMI is established if a marker has been released.

Presentation of Unstable Angina

Rest Angina : Angina which usually prolonged >20 minutes.

New onset Angina : Angina with Canadian Cardiovascular Society (CCS) class III severity.

Increasing Angina : Previously diagnosed Angina that has become distintly more frequent, longer in duration or lower in threshold (i.e increased by ≥ CCS class I to at least CCS class-III severity).[2]

1. **Dr. Sufia Rahman,** MRCP, FRCP, FACC, Dip-Card (London), FCCP, Professor of Cardiology, NICVD.
2. **Dr. Kazi Atiqur Rahman,** MBBS, MD (USA), MD (Cardiology), Assitant Registrar, NICVD.

Presentation of Non-ST Segment Elevation Myocardial Infarction

NSTEMI differs from UA primarily in severity and presentation.Angina usually occurs at rest. Ischaemia is severe enough to cause sufficient myocardial damage to release detectable quantities of a marker of myocardial injury, although cardiac markers or enzymes may not be elevated until several hours after onset of chest pain. ECG usually shows ST-segment or T wave changes and these changes may be persistent.

Initial Evaluation

Clinician evaluating a patient with chest pain must address the answer of two questions :

1. Are the sign and symptoms represent ACS secondary to obstructive CAD?
2. If yes then what is the likelihood of an adverse clinical outcome?

Table I. Likelihood that sign and symptoms represent an ACS secondary to CAD.[3]

Feature	High Likelihood. Presence of any of the followings	Intermediate Likelihood. Absence of high likelihood features and presence of any of the followings	Low Likelihood. Absensece of high or intermediate likelihood feature but may have
History	Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina, known history of CAD, including MI	Chest or left arm pain or discomfort as chief symptom. Age >70 years, male sex, diabetes mellitus.	Probable ischemic symptoms in absence of any of the intermediate likelihood characteristics. Recent cocaine use.
Examination	Transient MR, hypotension diaphoresis, pulmonary edema, or rales.	Extracardiac vascular disease.	Chest discomfort reproduced by palpation.
ECG	New, or presumably new, transient ST-segment deviation (≥0.05 mV) or T-wave inversion (≥0.2mV) with symptoms.	Fixed Q waves, abnormal ST segments or T-waves not documented to be new.	T-wave flattening of inversion in leads with dominant R waves, Normal ECG.
Cardiac markers	Elevated cardiac TnI, TnT, or CK- MB	Normal.	Normal.

Early Risk Stratifiction

Patient who presents with chest discomfort should undergo early risk stratification that focuses on anginal

symptoms, physical findings, ECG fingdings and bio-markers cardiac injury.

Table II. Short term risk of Death or nonfatal MI in patients with UA[3]

Feature	High Risk At least One of the following features must be present.	Intermediate Risk No high-risk feature but must have One of the following features.	Low Risk No high-or intermediate-risk feature but may have any of the following features.
History	Acelerating tempo of ischemic symptoms in preceding 48 hrs.	Prior MI, Peripheral or Cerebrovascular disease,or CABG, prior aspirin use.	
Character of pain	Prolonged ongoing (>20 minutes) rest pain	Prolonged (>20 minutes rest angina, now resolved, with moderate or high likelihood of CAD Rest angina (>20 min) or relieved with rest or sublingual NTG	New-onset CCS Class III or IV angina in the past 2 weeks without prolonged (>20 min) rest pain but with moderate or high likelihood of CAD
Clinical findings	Pulmonary edema, most likely due to ischemia. New or worsening MR murmur, S_3 or new/worsening rales, hypotension, bradycardia, tachycardia Age > 75 years.	Age >75 years	
ECG	Angina at rest with transient ST-segment changes >0.05 mV Bundle-branch block, new or presumed new sustained ventricular tachycardia	T-wave inversions >0.2 mV pathological Q-waves	Normal or unchanged ECG during an episode of chest discomfort
Cardiac markers	Markedly elevated (e.g., TnT or TnI >0.1ng?ml.)	Slightly elevated e.g.,TnT >0.01 but <0.1ng/ml.)	Normal

Symptoms not Characteristic of Ischemic Chest Pain

- Pleuritic pain (i.e sharp or knife like pain during respiratory movements in cough).
- Primary or sole location of discomfort in the middle or lower abdominal region.
- Pain that may be localized by the tip of one finger particularly over left ventricular apex.
- Pain reproduced with movement of palpation of the chest wall or arms.
- Constant chest pain that lasts for many hours.
- Very brief episodes of chest pain that last a few seconds or less.
- Pain that radiates into the lower extremities.

Typical symptoms of IHD raise the probability of CAD, features not characteristic of chest pain such as sharp stabbing pain or reproduction of pain on palpation do not exclude the possibility of ACS. In multi-center chest pain study acute Ischemia was diagnosed in 22% of patients who presented to the emergency room with sharp or stabbing pain and in 13% of patients with pain of pleuritic qualities. 7% of patients whose pain was fully reproduced with palpation were ultimately recognized to have ACS.[4]

Physical Examination

Vital sign should be measured in every patient with suspected ACS. Blood pressure should be measured in both arms, heart rate and temperature should be recorded during cardiovascular and chest examination and to see rales, S_3 gallop or the development of MR. Examination of peripherial vessels can also provide important prognostic informaiton.

Tools for Risk Stratification

ECG-Serial ECG should be done in every patient. ECG not only help in diagnosis of CAD but also provide prognostic information.[5]

Biochemical Cardiac Markers

Detection of biochemical cardiac markers from peripheral circulation are useful for both diagnosis of myocardial necrosis and the estimation of prognosis. Troponin T, Troponin I and CKMB are the most common markers usually measured.

Management

After a careful review of the history, physical examination, initial 12-lead ECG and biochemical cardiac marker definite diagnosis of ACS should be made.

Patient with definite ACS having ongoing chest pain, positive cardiac markers, new ST-segment deviation, new deep T-wave inversion, hemodynamic abnormalities or a positive stress test should be admitted at hospital

Possible ACS are those who had a recent episode of chest discomfort at rest not entirely typical ischemia but are pain free when initially evaluated, have normal or unchanged ECG and have no elevation of cardiac markers should have a stress test to provoke myocardial ischemia and if stress test is positive, diagnosis of ACS is confirmed.

All patient with definite ACS should have I.V. line and will get :

Anti-Ischemic Therapy

Bed rest with continuous ECG monitoring :

Nitroglycerine (NTG) spary sublingually followed by intravenous administration, for the immedite relief of ischemia and associated symptoms.

Oxygen administration for cyanosis and respiratory distress.

Morphine sulphate intravenously can be given when symptoms are not immediately relieved with NTG or when acute pulmonary congestion with LVF and or severe agitation is present.

Use β-blocker, with the first dose administered

intravenously if there is ongoing chest pain, followed by oral administration in the absence of contraindiction. β-blocker reduce myocardial oxygen consumption through their negative chronotropic and negative ionotopic action. All β-blocker can be used except those having intrinsic sympathomimetic action, and all are equally effective.

Patient with continuing or frequently recurring ischemia when β-blocker are contraindicated (eg. Bronchial Asthma), a nondihydropyridine calcium antagonist (e.g Diltiazem) can be used in the absence of severe LV dysfunction or other contraindication.

ACE inhibitors can be added when hypertension persist despite treatement with NTG and a β-blocker in patients with LV systolic dysfunciton or congestive heart failure and in ACS patients with diabetes.

Anti Platelet and Anti coagulant Therapy

Platelet plays a vital role in ACS and inhibition of platelets activity by aspirin should be initiated promptly. Aspirin is the first choice for anti platelet activity and give loading dose of non enteric formulation 162-325 mg as soon as possible if not aspirin sensitive. For continuous anti-platelet activity use either enteric or non-enteric formulation of aspirin 75-150 mg daily indefintely.

For aspirin sensitive patient or one who has major gastrointestinal intolerance can take clopidogrel or ticlopidne suitable alternative of aspirin.

Parenteral anticoagulant with intravenous Unfractionated Heparin (UFH) or subcutaneous Low Molecular Weight Heparin (LMWH) should be added to anti platelets therapy.

Table-3 Recommendations for Anti thrombotic therapy[1]

Antithrombotic Therapy

Possible ACS	Likely/Definite ACS	Definite ACS with Continuing Ischemia or Other High-Risk Features or Planned Intervention
Aspirin	Aspirin + Subcutaneous LMWH or IV heparin	Aspirin + IV heparin + TV platelet GP IIb/III a antagonist

If the patient has ongoing chest pain and hemodynamic instability despite getting all these medication in full recommended doses then plan for an early invasive strategy that involves - Coronary Angiogram (CAG) followed by coronary revascularization for suitable lesion either by percutaneous coronary intervention (PCI) method or surgical method, Coronary Artery Bypass Graft (CABG). These procedures can improve prognosis, relive symptoms, prevent ischemic complication and improve working capacity.

Discharge from Hospital

After physical and hemodynamic stabilization patient should be discharged at home with the advice of-
Risk factors modification
Appropriate medical regimen.
Cardiac rehabilitation

Regular follow-up

At each follow-up, Instruction should be given regarding-
Risk factors modification :

Smoking cessation.
Hypertension control.
Strict control of hyperglycemia.
Cholesterol reduction-Adding lipid lowering agent if LDL >130mg/dl
Regular exercise.

Conclusion

Although numerous modalities of treatment available for patient with UA and NSTEMI and all are effective in preventing complications like recurrent Ischemia, MI and Death, ultimate selection of treatment depends on socio-economic condition of the patient, cost-effectiveness and above all the benefit of treatment for the patient.

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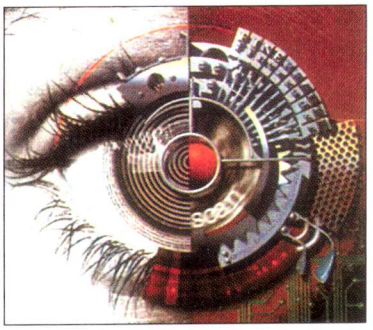
The Blind Shall See

Insert a Microchip to gain vision

Researchers around the US are working to develop an artificial retina that may restore sight to the blind.
In a healthy eye, the light- sensing cells of the retina (the fine membrane in the back, inside wall of the eyeball) convert light to electrical impulses. When these cell, which are called rods and cones, are damaged by diseases such as retinitis pigmentosa or age- related macular degeneration, the result is blindness. Researchers from Optobionics in Wheaton, IL, have developed and implanted the first artificial retina in six volunteers so far. This clinical trial can evaluate as many as 10 people in a 2 year U.S. FDA- approved safety study scheduled to end in June 2002.



Optobionics's Artificial Silicon Retina is a self- contained silicon microchip a little larger than the head of a pin with the thickness of human hair. It's implanted into a pocket under the retina. The chip is powered from the light that enters your eye. The other type of electric retina under development requires the use of a camera mounted within a pair of glasses and an outside processor to capture and transmit images to the microchip implanted on the retina. An artificial retina could be available within 5 years, experts say.

Source : Health & Nutrition, March 2002.

Hemophilia in Pediatric Surgery : A study in a Hospital, Bangladesh.

Mahbub-Ul- Alam

Summary

30 patients of hemophilia were admitted in pediatric surgical unit in Sir Salimullah Medical College, Mitford Hospital, Dhaka, Bangladesh from September, 1995 to December, 2001. Of which 15 (50%) patients had severe hemorrhage following circumcision, 25% (9) patients of this group had their circumcision by Hazams (quacks only perform circumcision), rest 25% (3) cases were done by registered doctors (MBBS) at their chambers, upazilla health complex and even in district hospital without any examination of bleeding and clotting time. 7 (23.35%) patients presented with uncontrolled bleeding from different sites of the body due to injury. 3 (10%) patients were the patients of hemarthrosis of knee and elbow joints. Another 3 (10%) patients presented with history of fresh bleeding per rectum without any pathology in anal canal, rectum and large intestine. 2 (6.65%) patients had hematuria. Prolonged clotting time was the diagnostic criteria. Fresh blood transfusion was needed in 5 (16.66%) cases due to delayed hospital attendance with severe anaemia. Only in 2 (6.65%) cases factor VIII was given. Aminocaproic acid and tranexamic acid was applied in every cases in intravenous or oral route. Surgical treatment was done in few cases. There were 2 (6.66%) death in this study.

Introduction

Hemophilia is a keen caring disease in case of male pediatric surgical patients. There is no statistical data of hemophilic patients in Bangladesh. In India 1 in 5000 male is hemophilic and each year 1300 children are born with this hemorrhagic disorder . There are nearly 50,000 patients with severe hemophilia A at present[1]. Data will be more or less same in our country. There are 20,000 hemophilic in the United States[5]. People of our country not at all aware of this disease. Manifestation starts after the circumcision when hemorrhage could not be stopped by usual procedures. So, early detection is possible in our country. But picture is quite different in other developing country where circumcision is not a compulsory religious custom. It is fact that only 3 to 5% of the affected people of this disease have the adequate resources and access to the medical treatment in South East asia[3]. In developed country greater availability and use of cryoprecipitates and factor concentrates has greatly improved and the management of hemophilia with an overall reduction in the morbidity and mortality. Combined development of comprehensive hemophilia treatment centers there has been a remarkable change in the outlook for these patients. So, these patients have near normal life but in developing countries the management of these patients continue to be a major problem.

1. **Dr. Md. Mahbub-Ul- Alam,** FCPS, FICS,
Associate Professor, Pediatric Surgery,
Sir Salimullah Medical College, Mitford Hospital, Dhaka.

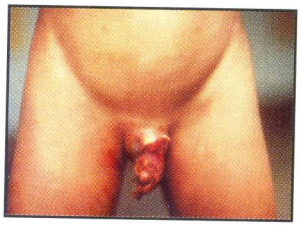
Table -1. Types of different presentations of hemophilic patients.

Types of presentations	Number (n = 30)	percentage
Bleeding after circumcision	15	50%
Bleeding from different sites of the body	7	23.65
Hemoarthrosis	3	7
Fresh bleeding per rectum	3	10
Persistent bleeding from the teeth	2	6.35

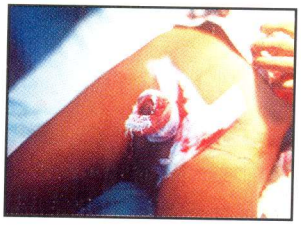
Methods, Materials and Managements

It was a retrospective study. 30 patients of hemophilia were admitted in pediatric surgical unit of Sir Salimullah Medical college, Mitford hospital, Dhaka from September,1995 to December 2001. In this study Hemophilia A and B could not be isolated.

50% patients were presented with bleeding after circumcision. 75% of circumcisions were done by HAZAMs ,quacks usually practice in rural area .They only performs circumcision.They also known as KHALIFA in some rural area. Rest 25% cases were done by registered doctors at their chambers, upazilla health complex or district hospitals. Not a single investigation was performed in any of the cases. The patients were in continuous bleeding.They tried locally to control it, but in vain. At last patients were referred to medical college hospital.



Hemophilia with hemorrhage on the 2nd post operative day.



Post circumcisional hemorrhage due to hemophilia.

Circumcission done by Hazam	75%
Circumcission done by Doctor	25%

7 Cases presented with nonstop bleeding from the different sites of the body due to trauma.Trauma were mainly from fall, injury by the hard toy, sharp edge of the furnitures, bitting of the tongue and lips.These injuries were more in case of toddlers and children. Surgical trauma was also an important factor.

In blunt trauma, one boy presented with a big hematoma in the left thigh.It was increasing day by day and responding to conservative treatment.In surgical trauma and punctured wound bleeding was not stopped. No investigations even BT,CT were done in any patients. As soon as the patients were admitted in hospital, hemophilia was suspected

Table II : Types of trauma

Types of trauma	Number
Surgical trauma	2
Blunt trauma	3
Punctured wound	2

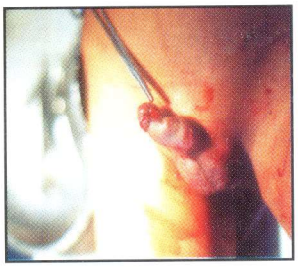
Table III: hemarthrosis

Types of trauma	No	Joint involved
Trauma	2	Knee and elbow
No trauma	1	Knee

Patient showing tongue representing anaemia.

3 patients presented with hemarthrosis.This occurred spontaneously in one case and in 2 cases following a minimal unforgettable trauma.

The joints were swollen and warm and had restricted movement. Irritability, guarding and limitation of movement of the affected joints were present in a 3 years boy.

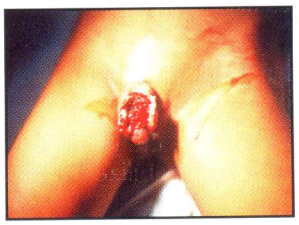


Hemorrhage due to hemophilia

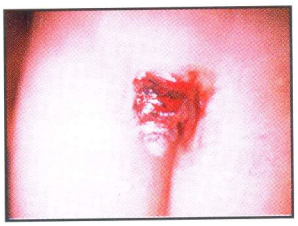
3 patients presented with fresh bleeding per rectum which was painless.Digital examination revealed nothing. Proctoscopic findings were normal.Medical treatment for different types of dysentery were failed. Colonoscopy done but it was completely normal. Blood examination confirmed the diagnosis. 2 boys were presented with continuous bleeding from teeth.

Results and Management

Patients with post circumcisional bleeding usually admitted average 2 to 5 days after the procedure. None of the patients had any investigations even BT, CT. The surgeons tried to stop the bleeding in various procedures such as tight dressings, applying gauge tourniquet around the root of the penis, re-suturing, ligation of blood vessels. When all attempts failed, patients were referred to the hospital. All the patients were anaemic.Just after receiving patients, blood was sent for grouping and crossmatching. At the same time BT,CTs were done. Factor VIII estimation was not possible. Tight dressings, dirty clothes were urgently removed. Clean dressings were applied. Where there was any clot formation and dressings were very much adherent to the wound, we didn't try to make it clean. Intravenous fluid was started. First we gave aminocaproic acid and tranexamic acid. They inhibited plasminogen and thus prevented the lysis of the clot. The dose of aminocaproic acid was 100mg/kg body wt every 6 hours intravenously and tranexamic acid 25mg/kg body wt orally or 10mg/kg body wt intravenously every 6-8 hours. At the same time, when bleeding didn't stop within one hour, we started fresh blood transfusion. 75% of the patients responded with this treatment. Rest 25% patients were sent to operation theatre for exploration of the wound. Under general anesthesia dressings were taken out and stitches were off to see any bleeding. These were ligated. But where we didn't get any bleeding vessel, we usually applied continuous suture between skin and the mucous membrane of the penis. The patients were kept 4 to 7 days for observation. We didn't use any diathermy. In 2 patients of post circumcision bleeding, factor VIII was given keeping in mind that 80% of all hemophilia patients have factor VIII deficiency which was a classical hemophilia.



4th Post operative haemorrhage due to hemophilia



Hemophilia

Dosage calculation of factor VIII

One unit of factor VIII per kilogram of body weight increases the factor VII activity by 2%.It has biological half life of 8 hours.The amount of factor required is calculated as :

$$\text{Factor VIII dose} = \frac{\text{\% rise required X body weight}}{2}$$

Skin laceration in hemophilia was treated on same line as normal persons. We sutured the gap when it was necessary by silk or catgut. Sometimes we applied sterile adhesive like Duoderm or Nishipore. When there was no gap and stitches were not required ,ice wrapped in thick cloth was applied immediately at the local site to control bleeding. Gauge soaked in dilute adrenaline (1 : 10,000 dilution) used for tropical hemostasis. At the same time aminocaproic acid was also tried. Result was good.

Hemarthrosis cases were managed as follows :

1) By keeping the joint in position of least pain along with application of ice pack

2) Elevation of affected limb
3) Immobilization of the joint in functioning position
4) To relieve the pain ,analgesics like paracetamol was given.
5) Aspirin was never given , because it absolutely contraindicated.
6) Physiotherapy was initiated as soon as the pain subsided to strengthen the muscles , stabilized the joint and to prevent contracture.

In hematuria aminocaproic acid or tranexamic acid should not be given as it stabilizes the clots which may result in clot colic.

During discharge we give advises to the guardians of all the patients as follows :

1) Life of the children needs to be adjusted to minimize the risk of trauma
2) Soft plastic toy should be given for playing
3) All intramuscular injections are contraindicated and injection should be given intravenously or subcutaneously
4) Child should not be left unattended in an infant seat or on a raised unprotected beds
5) Protective elbow and knee pads can be used.
6) Furniture with sharp edges must be avoided or the edges be padded . Minimum furniture should be kept in house.
7) Sports like swimming, badminton, fishing and walking have minimal risk while basketball, cricket and jogging have moderate risk, football, high and long jump have the greater risk. The risk of injury can be reduced with proper training, protective clothes and equipments.

Discussion

Hemophilia A and B are the sex-linked recessive bleeding disorders caused by decreased levels of functional procoagulant factors VIII and IX, respectively. Approximately, 80% of all hemophilia patients have factor VIII deficiency. The remaining 20% have factor IX deficiency which is called Christmas disease. But in our country it is very difficult to measure both the factors, for that reason we must depend on the simple test of clotting time.

In our religion,it is a rule to perform circumcision in the children.The most of circumcisions are performed by village quack without knowing coagulation status of blood.Even the registered practitioner who usually performs circumcision doesn't do this investigation. Problem starts with them. (Fig - II &III) Hemophilia is diagnosed in our country after manifestation of bleeding after circumcision which cann't be controlled by usual procedure of hemostesis.(Fig-IV,V) Bleeding problems during operation were not observed but 23% of all serious operations were complicated by post-operative hemorrhage[4].

Hemophilia patients are classified into three categories based on their level of circulating procoagulant.

1) Severe hemophilic - circulating procoagulant factor VIII is less than that of 1% high risk hemorrhage. Usually needs replacement therapy[5,6].
2) Moderate hemophilic- circulating procoagulant level is 1 to 5% .Spontaneous hemorrhage occurs infrequently .
3) Mild hemophilic - procoagulant levels more than 5%,rarely have bleeding problems and most have problems only major trauma or surgery[5,7].

In this study mostly the patients were of mild and moderate type of hemophilic (Fig-VI &VII). But confirmation could not be done due to lack of investigation facilities, financial constrains, devoid of knowledge of seriousness of the disease. Death was 2. Because those were the cases of moderate and severe hemophilia. These are also very difficult to manage even in the most developed country like USA or UK.

The management of this type of patients requires close co-operation among the surgeons, hematologists, pediatricians, and blood bank personnel[8]. Regarding any surgery careful pre-operative planning is essential. Fresh blood is to be kept ready. If possible adequate supply of clotting factor must be there. Patient must be admitted in the hospital a day before surgery. A bolus dose of factor VIII must be given.If there is per -operative hemorrhage fresh blood to be transfused.If there is any drainage ,the amount of collection must be monitored. In hemophilia after a minor surgery like circumcision, patient should be kept in hospital at least for a week. But for major surgery in our country, it is very difficult to manage all these patients. Because facilities are very poor . Factor VIII is very costly. Drugs like titre inhibitor porcine factor VIII, prothrombin complex concentrates (PCC) or activated PCCs such as autoplex or FEIBA are not available here. In the field of management of hemophilic patients especially moderate and severe type we are still in the primitive stage.

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Viral Bronchiolitis : An update on a recent epidemic

ARM Luthful Kabir[1], M Ruhul Amin[2], AKMA Morshed[3], M Shirin[4]

Introduction

Bronchiolitis is the most significant respiratory illness of infants and young children that occurs in the first 2 years of age usually causes by Respiratory syncytial virus (RSV) and is characterized by coryzal symptoms followed by rapid onset of cough, wheeze, fever, tachypnea, chest recession and crepitations, with radiological evidence of hyperinflation.[1,2]

Epidemiology

The incidence of bronchiolitis has been shown to be as high as 11 cases per 1000 children per year of both the first and second 6 months of life.[3,4]

Seasonality of bronchiolitis caused by RSV virus is striking and predictable. The incidence peaks during winter and early spring and reaches near zero in late summer and autumn in both hemispheres.[9] The age for peak incidence of RSV bronchiolitis is between 2 and 6 months; approximately 80% of all cases occur during the first year of life.[5]

Risk factors

Prematurity is a risk factor for severe lower respiratory tract illness (bronchiolitis, pneumonia) that necessatiates hospitalization[6]. Bronchiolitis is more common in boys[4,7], Rates of hospitalization with RSV bronchiolitis is more in lower socioeconomic families[8]. Breast feeding seems to protect against RSV and other wheezing respiratory illnesses in the first four months of age[9]. Infants who reside in crowded environment and have older siblings may be at risk of bronchiolitis[9,10].

Exposure to passive smoking, particularly maternal smoking, has been shown to be a risk factor for bronchiolitis in infancy.

Pathogenesis

RSV is transmitted by direct inoculation of large droplets or by self-inoculation[11]. Once the RSV infects the eyes or nose the incubation period is 2 to 8 days. The susceptibility of infants and young children to bronchiolitis is partly as a result of their immunological immaturity and smaller airways. The pathological findings associated with bronchiolitis include: epithelial cell necrosis and desquamation; edema of the bronchiolar walls; mucus plugging of airways and peribronchiolar infiltration with lymphocytes.[12] These pathological changes cause hyperinflation of the lungs, increased airway resistance, decreased compliance and an increased work of breathing. The non-uniform distribution of the pathological events cause ventilation-perfusion mismatching which results in hypoxaemia. Severe bronchiolitis may result in respiratory muscle fatigue, hypoventilation and carbondioxide retention.

Aetiopathogens

Infectious agents associated with acute bronchiolitis

Infectious agents	Relative frequency (%)
Respiratory syncytial virus	>50
Parainfluenza viruses	25
Adenovirus	5
Rhinoviruses	5
Influenza viruses	5
Enteroviruses	2
Herpes simplex virus	2
Mumps virus	<1

Clinical feutures

Symptoms and signs in children with acute bronchiolitis (%)

Symptoms/ signs	114 cases	221 cases
Coughing & Wheeze	100	100
Unable to feed	66	91
Fever	71	92
Fast breathing	93	99
Chest indrawing	93	98
Crepitations	78	92
Hyperresonance on percussion	40	–
Palpable liver	–	84
Palpable spleen	–	37
Grunting	18	–
Cyanosis	5	3
Toxic appearance	–	3
Hoarse voice	–	4
Convulsion	–	2

Investigations

- Measurement of oxygen saturation by pulse oximetry is widely used to see the oxygen saturation level in blood.
- Total leukocyte count (TLC) is usually normal in most of the cases.
- CXR-ranges from normal to an extensive spectrum: hyperinflatation of the lungs with patchy areas of atelectesis and increased AP diameter on lateral view

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showing fullness of the retrosternal space.

- Blood gas analysis is done to look into respiratory acidosis or hypercapnea. Nasopharyngeal aspirates (NPA) can be tested directly for RSV antigen within few hours by ELISA or immunofluorescence.
- Serum electrolytes, can be done to see the effect of inappropriate secretion of ADH.

Diagnostic criteria

Most authors agree that the following features are adequate for the diagnosis of bronchiolitis.

* Child below two years (preferably one year) of age
* Previously healthy child's
* Wheezing (Preceded by Coryzal Symptoms)
* Hyperinflation of the lungs on chest x-ray

Differential diagnosis

The common differential diagnosis are :

* Viral pneumonia
* Bacterial pneumonia
* Pertussis
* Congestive heart failure
* Infantile asthma

Management

When to be hospitalized ?

* Toxic appearance
* Unable to feed
* RR 60 to 70/ min
* Cyanosis
* Hypoxaemia- SaO_2<90% as measured by pulse oxymeter

Supportive Management

The traditional approach to symptomatic management of bronchiolitis has been supportive care with attention to oxygen therapy, hydration and respiratory support as needed.

* Isolation of the case as a contagious disease
* Placed in a congenial and cool environment without too much wrapping
* Positioning of the infant-head up, sitting at a 30 to 40 degree angle or with the head and chest slightly elevated so that the neck is somewhat extended
* Hydration (dehydration because of cough-induced vomiting, poor intake or breathlessness)+by oral plus IV fluids.
* Feeding may be given through nasogastric tube and breast feeding must be continued
* Monitoring of HR, RR, body temp, electrolytes, osmolality, pH and clinical signs of deterioration

Specific Management

* Humidified oxygen administration in concentrations of 35 to 40% is adequate for most patients to maintain arterial saturation in the range of 90-95%.
* Antibiotics have little therapeutic value in bronchiolitis. Bacterial infections are rare in bronchiolitis. Antibiotic therapy (as per WHO guideline for ARI) may be initiated if the child is toxic, febrile, shows high TLC (>15,000/cmm) and lobar infiltrate on radiography.
* Nebulized salbutamol and systemic corticosteroid have limited therapeutic value. They are useful only in cases having severe symptoms, H/O recurrent, wheeze, protracted course of illness and oxygen saturation <94%.
* Nebulized epinephrine is being increasingly recommended in relieving the symptoms of bronchiolitis.

Course and prognosis

The most critical phase of illness is first 48-72 hours of the onset of cough and dyspnoea. The natural course of bronchiolitis is remarkably constant. The duration of maximal respiratory distress is 1 to 2 days, followed by dramatic clinical improvement. The case fatality rate is below 1%. Death usually happens from prolonged apnoeic spells, uncompensated acidosis or severe dehydration.

Conclusion

* Viral bronchiolitis is a self-limited disease and treatment is mainly supportive.
* Oxygen therapy, hydration, feeding, keeping in a cool environment, isolation (preferable) are the mainstay of treatment .
* Nebulized epinephrine is being increasingly recommended to relieve symptoms.
* Nebulized salbutamol and systemic corticosteroid have limited efficacy.
* Antibiotic is indicated only when the child is toxic, febrile, shows high increase TLC (>15000/cmm) and lobar infiltrate in radiography.

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Nonstress test in high-risk pregnancy : Evaluation and Management.

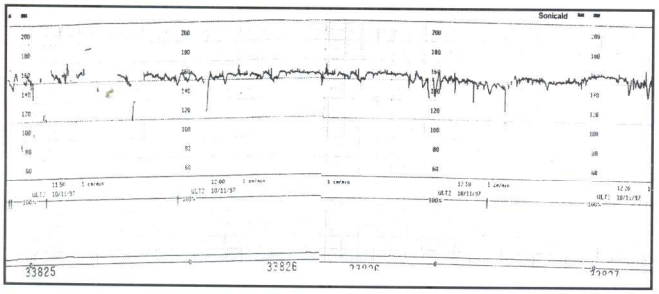
Mahfuz Ara Begum[1], Shahla Khatun[2]

Abstract

Evaluation of nonstress test (NST) in the antenatal assessment of fetal well being in the high-risk pregnancy has been found to be clinically efficacious. The basis for its interpretation has been the reactive or normal and nonreactive or abnormal test. Between January 1997 and May 1998, 53 high risk pregnant women were studied by NST at the Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University. Reactive group showed favourable fetal outcome and nonreactive showed significant increase in overall abnormal outcome, low 1- and 5- minute apgar score, small for gestational age infants subsequently admission into neonatal care unit and perinatal mortality. Based on our experience, the NST continue to be a valuable procedure for the assessment of fetal well being in our high risk pregnancies.

Introduction

The antepartum assessment of fetal well being has become an integral part of the management of any high risk pregnancy. In order to achieve this evaluation, varying biochemical and biophysical techniques have been described. The biophysical techniques, primarily the antepartum fetal heart rate testing (AFHRT) have enabled the clinician to immediately and reliably evaluate fetal status.



Non reactive nonstress test. No acceptable foetal heart rate acceleration over a 40-minute period

There is relationship between fetal movement and heart rate acceleration demonstrated by Rochard et al-[1] and Lee et al-[2]. They demonstrated acceleration of foetal heart rate associated with fetal movement in Rh isoimmunized babies where no stress factor was applied.

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Evertson et al-[3] demonstrated from several retrospective studies of potential for nonstress test (NST) and clearly defined repetitive acceleration and the absence of positive contraction stress test (CST) result. Therefore, NST may be defined as acceleration of fetal heart rate (FHR) in association with fetal movement when no external stress is applied.

Twenty one different standards for reactive NST showed that the most common criteria for reactivity was the presence of at least two times fetal heart rate acceleration of at least 15 cpm amplitude and of 15 second duration in any 20-minute epoch.[4] Mostly used other interpretive criteria and correlation between NST and diagnostic parameters, e.g-sensitivity, specification, etc.

The interval between tests was originally set 7day interval have shortened as experience evolved and performed twice weekly or often daily or even more frequently.[5]

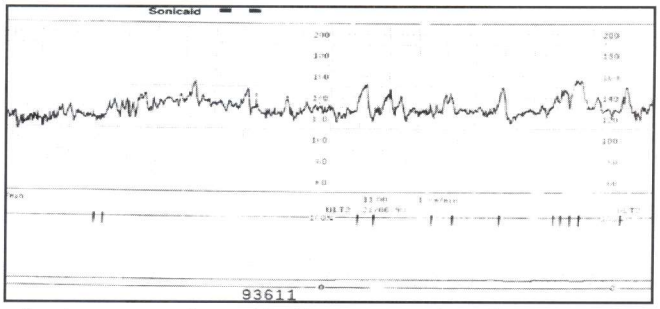
According to fetal sleep wake cycle as described by Pillai and James,[6] 40 minute testing time is standard for NST.

Continuous experience showed some limitations of CST. The main problems were the length of time required, 60-90 minutes, needed for intervening access usually hospital based, high incidence of suspicious or equivocal result, lack of specificity of positive result.

Materials and Methods

The present study was carried out in the Department of Obstetrics and Gynecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, during the period from January 1997 to May 1998.

Fifty two pregnant women whose pregnancies were



Reactive nonstress test. Incrase of foetal heart rate to more than 15 beats per minute for longer than 15 seconds following feotal movements, Indicated by vertical marks on the part of recoreding

categorized as high risk for uteroplacental insufficiencies were included in the study. Primary indications for antepartum evaluation by NST was postdated pregnancy, >42 weeks, clinically suspected intrauterine growth retardation (IUGR), chronic hypertension, preeclampsia, diabetes mellitus, history of stillbirth or intrauterine death

(IUD), less fetal movement, maternal heart disease, grade III and grade IV, Rh isoimmunization (Table I) when last antepartum test was done more then 7days of delivery and pregnant women with no apparent risk factors were excluded from the study.

Table -1. Indications for testing of the study population by major high risk factors presents.

Primaty high-risk factors for testing	Patients managed by nonstress test (n-52)	
	No.	(%)
Postdated Pregnancy	11	(21.0)
Intrauterine Growth retardation (IUGR)	8	(15.0)
Decreased Foetal Movement	11	(21.0)
Diabetes mellitus (all classes)	4	(8.0)
Preeclampsia/ chronic hypertension	10	(19.0)
Bad obstetric history	3	(6.0)
Rh isoimmunization	2	(4.0)
Others (Cardiac disease with grade III, Guillain - Barre Syndrome)	3	(6.0)

NST was performed with the use of cardiotocographic instrument (Sonicaid Meridian 800) with 2 MHz transducer. Patient was placed in semi recumbent position with slight left lateral tilt. Blood pressure was measured at the initiation of the test and contraction signal, chart printer was pressed to switch on. A button was given to the patient with the advice to press the button each time she felt fetal movement. This was allowed to continue until either a reactive pattern was demonstrated or after 40 minutes of the test. Test was then evaluated as reactive or nonreactive on the basis of result.

Clinical management of the study of the patients were based on fixed criteria.[3] If NST was reactive, it was rescheduled for repeat test on a week's time. If NST was nonreactive, repeated test was done within 24 hours. If NST showed persistent nonreactive pattarn, the patient was considered for delivery. In case of diabetes mellitus, test was done twice weekly. The overall clinical condition including gestational age, maternal condition were also considered. Induction of any labor and vaginal delivery were undertaken unless contraindicated by other obstetric factors, where caesarean section was done.

Measures of assessment of fetal outcome were considered as low apgar score in 1- minute and 5- minute after birth, <7 determined by independent observer score. Birth weight (2.5 kg after 36 weeks of pregnancy or <10th percentile of the gestational age.[7] Admission into neonatal intensive care unit (NICU) and stay for more than 24 hours for reasons other then prematurity, perinatal mortality. For the present study, outcome was considered to be normal if all of the above measures were absent. Abnormal outcome was considered to have occurred if any or all of the adverse conditions were present.

Result

Fifty two high risk pregnancies of different gestational age between 31-43 weeks were managed by NST. Postdated pregnancies were the most common indication. A total of 96 tests (mean 1.86 test per patient) were performed. All the patients delivered within 7days of their last antepartum test.

Table - II. Evaluation of foetal assessment by nonstress test for each of the different fetal outcome.

Table-II shows evaluation of fetal assessment by NST. Out of 52 patients, 42 had normal results, of which 7 had abnormal outcome. Ten patients showed abnormal

Outcome	Normal test result (n-42)		Abnormal test result (n-10)		X^2 Value	P Value
	Yes	No	Yes	No		
Overall abnormal	7	35	6	4	8.07	<0.01*
Low 1-minute Apgar score	3	39	3	7	4.13	<0.05*
Low 5 minute Apgar score	2	40	2	8	0.74	>0.05^{NS}
Small for gestational age	4	38	4	6	3.67	<0.05*
Admission into NICU	3	39	4	6	7.52	<0.1*
Perinatal Mortality	2	40	1	9	2.00	>0.05^{NS}

^{NS}Not significant

**Significant*

****Highly Significant*

Test Results have shown in number of cases.

test results and of them 6 showed abnormal outcome. There was significant differences between abnormal and normal test in predicting the overall abnormal fetal outcome. Low 1 minute Apgar score occurred on 3 occasions during 42 normal NST. Of the 10 abnormal NST, 3 infants were observed to have depressed evaluation. A statistically significant difference was observed when abnormal and normal NST results were compared. Low 5-minute Apgar score was observed in 2 infants of 42 normal NST results, and in 2 Infants, out of 10 abnormal NST results. Statistically significant difference was not observed when abnormal and normal NST results were compared.

Six Small for gestational age (SGA) infants were identified out of 42 normal test and 4 infants out of 10 abnormal NST Results. Statistically significant (P<0.01) difference between the abnormal and normal NST results were observed in predicting IUGR.

There 6 out of 42 normal NST infants and 4 out of 10

abnormal NST infants were admitted into NICU. A statistically significant (P<0.01) difference was observed

Table III. Perinatal Death in cases managed by nonstress test with delivery within 7 days of last test.

Time of death	Gestational age (weeks)	Indication for test	Test result day	Test to Delivery Interval	Causes of death
Neonatal Death	39	Diabetes mellitus	Normal	0	Shoulder dystocia Babies Weight 4.8 Kg Spontaneous labour
Neonatal Death	32	LFM for 3 days, pain L/A abdomen with two previous C/S	Normal	1	Died 7 hours after delivery Babies Weight 1.3 kg >10th percentile
Neonatal Death	36	Severe Hypertension with severe IUGR	Abnormal	1	Asphyxia and IUGR babies weight 1.3 kg <10th percentile

IUGR = Intrautenine growth retardation

when abnormal and normal NST results were compared.

Out of 42 normal NST results, there were 2 neonatal deaths. In case of 10 abnormal NST results, there was only 1 neonatal death. There was no statistically significant difference between abnormal and normal test results.

Discussion

In this study, NST when reactive does represent a satisfactory indicator for fetal well being and nonreactive test shows fetal jeopardy in the form of significant increase in abnormal outcome of foetus, increases in low Apgar score, SGA infants, admission in to NICU and perinatal mortality. Incidence of abnormal test was higher (19-23%) that other study[8,9], but similar to Phelan[10], the reason for higher incidence of abnormal test seem to be due to inclusion of high risk cases which were genuine because strict standard was maintained to include patients in the study. There were also interobserver and intraobserver variation in interpretation of test results. There were also differences in the criteria for interpretation of tests in different studies.

Prognostic value of normal and abnormal test results in respect to low 5- minute Apgar score (<7), abnormal test was not more predictive of low 5- minute Apgar Score than normal test, which differ from Platt et al[9]. The reason may be low sensitivity of low 5 minute Apgar score is highly subjective and may not always be measured accurately at 1- and 5- minute.

Among 3 neonatal deaths, 2 showed normal test results, but death occurred due to shoulder dystocia in one and in the other, due to prematurity. The neonatal death showing abnormal result was due to 36 week pregnancy with severe hypertension with severe IUGR.

From the present study, it may be concluded that NST does represent a clinically reliable technique for

Table -IV

Performance characteristics of non stress test for overall abnormal outcome and each of the different fetal outcome parameter in percentage (n = 52)

Out come	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity
Overall abnormal out come	60.00	83.33	45.50	89.74
Low 1minut Apgar Score	30.00	92.85	50.00	84.78
Low 5 minutes Apgar Score	20.00	95.23	50.00	83.33
Small for gestational age	40.00	85.71	40.00	85.71
Admission into NICU	40.00	92.85	57.14	86.66
Perinatal mortality	00	95.23	33.33	81.63

Table IV shows the sensitivities, specificity, positive predictive value and negative predictive value of overall abnormal out come and each of the different fetal out come parameter.

antepartum assessment of fetal well being. However, it is suggested that further study with large sample size should be carried out.

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Perforated Gas Containing Hollow Viscus : A study in a Hospital, Bangladesh

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Summary

During the period from May 2001 to December 2001, a total number of emergency admissions in surgery unit -V. of DMCH was 450. Out of them 100 were due to perforated gas containing hollow viscus (Table-1), majority of them were from duodenal ulcer (72%),10% from typhoid ulcer, 06% from intestinal tuberculosis and the remaining were from other causes (Table-7). 84% were male and 16% were female (Table-3), 60 were of age between 21-40 yrs (Table-2). All of the patients presented with pain in the abdomen, 64% with vomiting, 72% with abdominal distension, 44% were febrile, 6% with shock (Table-4). 80% of patients were of low socio-economic status, 74% were smoker, 84% were involved in stressful job, 60% of irregular dietary habit and 72% perforation developed in fasting state (Table-10). Most of the patients attended after 6 hours of onset of symptoms,14 came after 24 hours, two even came after 12 days (Table-5). 94 were surgically treated , of which 60 were recovered uneventfully, 30 developed complications and 4 died post-operatively (Table-11,12). On 50 patients repair with omental patch was performed, others were managed by different techniques including definitive surgery in some cases (Table-9).

Introduction

Perforation of gas containing hollow viscus still covers a large number of hospital emergencies in our country despite the improvement of diagnostic and treatment facilities of the conditions causing this problem. It is a leading cause of morbidity and mortality in all age group in our country. It constitutes a serious surgical emergency which needs early surgical intervention after adequate resuscitation and no doubt in all aspect, time spending from occurrence of perforation to operation is the most important factor for it's management. It is also important that in all sorts of cases a surgical expert with a dependable team which can support the preoperative and post-operative situations adequately is needed to decrease both the morbidity and mortality of patients significantly. Clinical examinations supported by simple radiology is almost sufficient to take decision for laparatomy as a case of perforated gas containing hollow viscus. But cause may be so diverse that only simple repair may not be the justified surgery in all cases. If general condition of the patient and other situations permit definitive surgery for the preexisting causative factor can be performed successfully during the same sitting.

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Materials and Methods

In our current study 100 different types of perforated cases who were treated in su-5 of DMCH after admission through emergency dept. during the period from May - October, 2001 were considered. Patients who had positive findings after laparatomy with those who had not undergone surgery but diagnosed clinically and radiologically were included in this study. Patients died both pre-operatively and post-operatively also included. Thus a total of 100 patients were studied ultimately.

Clinical findings with radiological supports and in few cases four quarter peritoneal taping was the diagnostic techniques. In some cases laboratory investigations like Hb% ,serum electrolyte, urea, creatinine, ECG were performed. Blood grouping done in all cases. Proper resuscitation including fluid and electrolyte balance, correction of anaemia by blood transfusion, antibiotics to control infection, management of shock was carried out in necessary cases. Children below 12 yrs. were not studied .

Result

During the mentioned period out of 450 total emergency admissions under surgery-v of Dhaka Medical College

Table -1

Incidence of perforated hollow viscus	
Total Nos. of emergency admission	450
Total Nos. of perforated hollow viscus	100
% of perforations among emergency admission	22.22

Hospital 100(22.22%) were perforated gas containing hollow viscus (Table -1). Of them 84 (84%) were male,16 (16%) were female; with a male-female ratio 5.02:1

Table -3

Sex incidence		
Sex	Nos. of cases	% of total numbers
Male	84	84
Female	16	16

(Table-3). Regarding age 5 were below 20 yrs. 30 were above 40 and 60 (60%) were between 21- 40yrs (Table-2). Males were mostly affected and middle-aged group people of low socio-economic class (80%) involved in

stressful occupation (84%) were main sufferer. 74 (74%) were smoker, 10 (10%) were H_2 blocker taker, 60 (60%) had irregular dietary habit, 4 (4%) had previous history of

Table -2

Age incidence		
Age	Nos.of cases	% of total cases
Below 20 yrs.	10	10
21-30	28	28
31-40 yrs.	32	32
41-50 yrs.	20	20
Above 50 yrs.	10	10

perforation of duodenal ulcer 72 (72%) were in fasting state during the time of perforation (Table-10).All presented with pain in the abdomen, 64 (64%) associated with vomiting, 44 (44%) with fever, 72 (72%)

Table-4

Symptomatology		
Symptoms	Nos. of cases	% of cases
Pain in abdomen	100	100
Vomiting	64	64
Abdominal distension	72	72
Fever	44	44
Shock	06	06

with abdominal distension and 6 (6%) presented with shock. None reported with hematemesis and malena (Table-4).

Radiologically skiagram of plain abdomen showed free gas under both domes of diaphragm in 8(8%) cases ,only under right dome in 80(80%) cases , only under left dome none and multiple gas shadow with fluid level in 8(8%) cases. In 4(4%) patients no free gas was found under any dome of diaphragm. (Table-6)

Table-6

Radiological Finding		
Plain abdomen in erect posture	**Nos. of cases**	**% of cases**
Free gas only under right dome of diaphragm	80	80
Free gas under both domes of diaphragm	08	08
Absence of free gas under any dome of diaphragm	04	04
Multiple gas shadow with fluid level	08	08

Table - 7

Aetiological finding to perforation		
Aetiology	Nos. of cases	% of cases
Peptic ulcer disease	72	72
Typhoid ulcer	10	10
Intestinal Tuberculosis	04	04
Traumatic	04	04
Drug induced (NSAID ,steroid etc.)	04	04
Cancer	02	02
Dengue Haemorrhagic shock syndrome	02	02
Others	02	02

Out of 100 patients 72 (72%) were due to peptic ulcers, 10(10%) due to typhoid ulcer, 4(4%) due to intestinal tuberculosis, 4(4%) were traumatic, 4(4%) drug induced, 2 was from dengue hemorrhagic shock syndrome and two was found from cancer (Table-7). Except one, all presented after 6 hours from the onset of symptoms; two presented even after 12 days. 36% came between 6-9 hrs, 28% between 9-12hrs. 20(20%) within 12- 24 hrs , others appeared after 24 hours (Table-5).

Table-5

Incidence of interval between time of perforation and time of operation		
Interval	Nos. of patients	% of patients
3-6 hrs.	02	02
6-9 hrs	36	36
9-12 hrs.	28	28
12-24 hrs.	20	20
1-3 days	06	06
3-7 days	06	06
7-14 days	02	02

On laparatomy peritoneal fluid shows billous appearance in 52(52%) patients, purulent in 44(44%) and 4(4%) were sero-sanguinous. None was found in stomach, 74(74%) were in the anterior wall of the 1st part of duodenum, 22(22%) jejunal and ileal, 4(4%) were in appendix (Table-8). All duodenal perforations were single, 22(22%) of

Table-8

Operative finding			
Basis	Finding	Nos. of cases	% of cases
Nature of peritoneal fluid	Billous	52	52
	Purulent	44	4
	Sero-sanguinous	04	04
-Site of perforation	Duodenum	74	74
	Jejunum	02	02
	Ileum	20	20
	Appendix	04	04
Size of perforation	<5 cms.	84	84
	5-10 cms.	16	16
Nos. of perforation	Single	80	80
	Multiple	20	20

jejunal and ileal showed multiple perforations, that in appendix was single. Size varies from 5-10 cms, in 16(16%), less than 5cm. in 84(84%) cases (Table-8).

Repair with omental patch carried out in most of the cases (50%) mainly for duodenal ulcer perforations. Other duodenal ulcers were managed by pyloroplasty (12) and trunkal vagotomy with gastro -jejunostomy (8). 4 ileal perforations were repaired simply and for others resection and anastomosis performed, ilostomy/ colostomy was done for 10, two was managed only by

Table-9

Operative strategy followed		
Types of operation	Nos. of cases	%of cases
Simple repair	04	04
Repair with omental patch	50	50
Pyloroplasty	12	12
Vagotomy and bypass	08	08
Resection and anastomosis	14	14
Ileostomy/colostomy	10	10
Only peritoneal toileting	02	02

peritoneal toileting as the perforation was found sealed (Table-9).

In regards to post operative complications 24 developed wound infection including 10 wound dehiscence and 10 fistula, 6 paralytic ileus, 4 pneumonia, 2 septicaemia which was died ultimately. Thus a total of 30 (30%)

Table-11

Post-operative complications (n=30)		
Complications	Nos. of cases	% of cases
Pneumonia	04	13.34
Paralytic ileus	06	20
Fistula	10	33.34
Wound infection	24	80
Wound dehiscence	10	33.34
Residual abscess	02	06.66
Septicemia	02	06.66
Others	02	06.66

patients developed complications of varying degrees (Table-11). Post-operative recovery was uneventful in 60 patients .

Two recovered non-operatively who developed residual

Table -12

Mode of dismissal from hospital (n=100)			
Mode		Nos. of cases	% of cases
Death	Operated	06	06
	Non-operated	04	04
Recovery	Un-complicated	60	60
	Complicated	30	30
	Operated	88	88
	Non-operated	02	02

abscess. A total of 10 (10%) patients died, among them 4 were pre-operative as presented with shock leading to irreversible state, 6 were post-operative(Table-12).

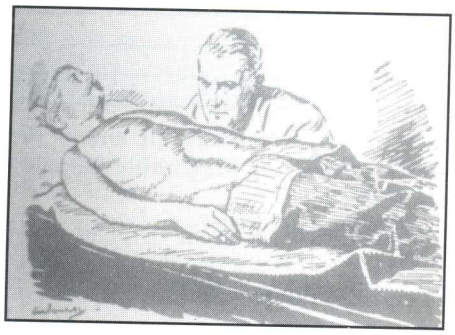
Discussion

Perforation of gas containing hollow viscus is a common emergency in our hospital admission. No doubt, peptic ulcer perforations are the leading cause and lot of studies have been carried out in this connection. Yet, other causes of perforation are not uncommon like typhoid, tuberculosis of intestine etc and though works have been done by some in concern to these diseases, particularly perforation as a complication of them has been studied minimum so far.

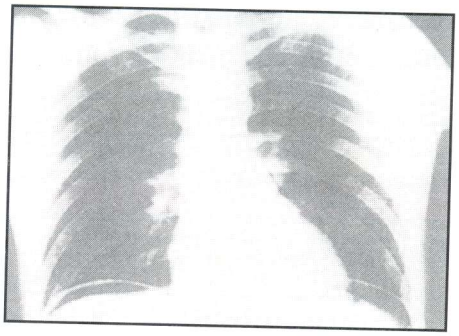
Table-10

Conditions associated with perforation		
Conditions	Nos. of cases	% of cases
Fasting condition	72	72
Irregular dietary habit	60	60
Smoking	74	74
Low socio-economic status	80	80
Stressful occupation	84	84
H_2 blocker taker	10	10
Previous perforation	04	04

In our study duodenal ulcer perforation emerged as the main aetiology (72%), whereas typhoid ulcer (10%), intestinal tuberculosis (4%), trauma (4%) etc, took significant part in perforating gastrointestinal tract. This study runs deemly parallel with the studies of Omer Alabaz et al, Viranuvatti and ZIA-UR et al. In all types of cases patients were mostly of low socio-economic status and males of middle age group were mainly affected. Leo D. Nannini worked on acute perforated peptic ulcers and observed that all were male, majority occurred between 40-60 yrs, sixty percent operated within six hours, simple closure was performed in all cases, no post-operative mortality was reported, 66.6% non-operative mortality, 20 developed complications, two-third was diagnosed by pneumoperitonium radiologically. Our observations only coincides with that study in respect to sex and age incidence and also an increased number of



A sketch of Mr. Hamilton Bailey watching for abdominal movement on respiration. In case of perforated peptic ulcer abdominal movement is restricted or absent



Plain x-ray of a perforated duodenal ulcer showing gas beneath the diaphragm.

complications. Late presentation and delayed operation due to spending of time for resuscitation increased the incidence of faecal fistula as well as morbidity and mortality significantly in our study. Duodenal ulcer perforations were repaired with omentoplasty instead of simple repair in almost all cases and 88% were diagnosed radiologically pre-operatively. In addition our analysis showed that irrespective of causes all patients presented with abdominal pain of varying severity. Vomiting, abdominal distension and fever were other striking features. Most of the duodenal perforations were associated with smoking, fasting state, irregular dietary habit and stressful occupation. Few were H_2 blocker taker and few had history of previous duodenal ulcer perforation. As only 20% were found hemo-dynamically stable during the time of operation underwent definitive surgery, others repaired. In comparison to others, complication was minimum after surgery, though two suspected duodenal ulcer perforation patient died non-operatively as presented with shock and delayed measure for resuscitation. In our observation typhoid ileal perforations almost always presented late, found multiple in number, complicated more and prolonged hospital stay due to development of fecal fistula, bed sore, electrolyte imbalance, wound infection and wound dehiscence. These cases were treated by resection of diseased part and end to end anastomosis mostly, only in few cases ilostomy was made. A.R.K. ADESUNKANMI studied 50 typhoid ileal perforations who had also same observations. Welch and Martin recommended wedge excision and segmental resection and end to end anastomosis because of frequent re-perforation in their patients. We had also intestinal tuberculosis, traumatic, drug induced, cancer perforation and one patient with dengue hemorrhagic shock syndrome who developed multiple gangrenous perforations of jejunum. Omar et al reported 5 of 67 patients of abdominal tuberculosis as complicated by perforation. Emran et al had a study about Dengue hemorrhagic fever but they did not report any perforation and so far we have no such report to our knowledge.

Conclusion

Although the treatment of peptic ulcer disease is improved by many folds, yet it's complications are not reduced to that comparison in our country. Still our major bulk of emergency operations comprise peptic ulcer perforations. By the same time perforation as a complication of other conditions like typhoid ulcer, tuberculosis, cancer and trauma of gut exhibit a significant number in our study, management of which required surgical skills as well as expert team approach. Patients reported with dengue shock syndrome needed intensive attention both pre and post operatively. However in almost all cases pain was the commonest feature. Though surgical strategy was different the basic principle of management was same in all sorts. Outcome was also different depending upon the underlying causes. From our study we have also experience that in case of traumatic perforations as it is very difficult to predict the extent or involvement of perforation pre- operatively a skilled surgical expert who can take decision judicially on the operation table is required. Instead of simple repair, resection and anastomosis of gut in case of typhoid ulcer perforation, conferred better result. Furthermore, interval between time of perforation and time of operation is the key factor for their management, irrespective of type of perforation and it is directly proportional to morbidity and mortality. With intensive care and close follow up two was salvaged though came 12 days after perforation. Thus it reveals that pre-operative and post-operative care is another important factor which can minimize the complication and reduce the mortality. So, we can conclude that, to manage a case of perforated hollow viscus of any sorts, a skilled surgical team which can handle these situations confidently is a prime importance.

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Carcinoma Breast : A study in an urban Hospital, Bangladesh

Yeaqub Ali[1], Syed G Kibria[2], M Nasimul Islam[3], M Mokhles Uddin[4], ASM Jahangir Chowdhury[5]

Summary

A clinical study of old and new 43 cases of carcinoma (Ca) breast were carried out at Radiotherapy Department, Faridpur Medical College Hospital, Faridpur from January '99 to June 2001 with a view to see the initial stage at presentation, to evaluate the modes of treatment, response to treatment and find out the survival period after presentation. All the cases were under follow up. Male 2.32% and female 97.68%, peak age incidence were (31-45 years) 48.84%, cytologically proved 90.70%, stages were I, II, III and IV 13.95%, 53.49%, 18.61% and13.95% respectively. Infiltrating ductal carcinoma 79.06%, adeno-carcinoma were 4.65%, medullary carcinoma 4.65%. Treatment completed only in 39.53% of cases. No evidence of metastasis were found in 69.72% cases after completion of treatment, and one year survival were 95.35%, 2.5 years survival were 81.39% and more than 5 years survival were 4.65% and expired 18.61%.

Introduction

Breast cancer is one of the most common malignant lesions and leading causes of death from cancer in women[1]. The incidence of different types of breast lesions varies from country to country depending on socioeconomic condition, living style, marital age, frequency of pregnancy and lactation habit[2]. breast cancer affects about one million women per year world wide. In general 1 in 12 women are affected.

Only about 1% of breast cancer occurs in males - about the same ratio as the amount of breast tissue[4].

Breast cancer is currently viewed as a systemic disorder, right from its outset varies widely in behavior within the same histological type. Hence, the need for a multi-disciplinary approach where locoregional treatment (surgery and radiotherapy) is accompanied by systemic (chemotherapy and hormone therapy)[5].

Surgery, cytotoxic chemotherapy, radiotherapy and hormone therapy can provide the hope of cure in early cases.

Materials and methods

This prospective study presents 43 cases of carcinoma breast, aged from 25 to 80 years. They attended at Radiotherapy out patient department, Faridpur Medical College Hospital from January '99 to June '01. All the cases were referred from different departments of this hospital and other hospitals. Thorough physical examinations were done and relevant data were collected from case sheets of the hospital records and all efforts were made to obtain maximum possible information regarding the duration of illness, mode of onset, clinical findings, evidence of metastasis, investigations procedures carried out, such as routine investigations; like routine blood examination, X-ray chest, USG of the whole abdomen, bone scan, liver scan, C.T. scan, cytology of the tumour cell (histo-pathology or fine needle aspiration cytology etc.) and confirmed the diagnosis, staging of the tumor were done by clinical staging of breast cancer system.

Out of 43 cases surgery were done in 42 cases and combination cytoxic chemotherapy (CMF) and loco-regional radiotherapy were provided only in 17 cases. Among 43 cases 4 patients were given neo-adjuvant chemotherapy (CAF therapy) followed by surgery after doing staging (from stage III A to stage II B) then continuation of cytotoxic chemotherapy (CMF cyclophosphamide, methotrexate and 5 Fluro-uracil) + locoregional radiotherapy and hormone therapy (Antiestrogen, Tab. Tamoxifen 20 mg orally daily for 5 years).

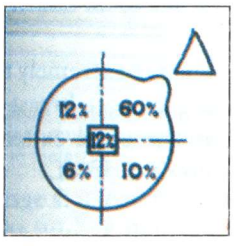
All the documents were recorded in individual printed sheets. At the end of treatment, they were evaluated periodically.

Results

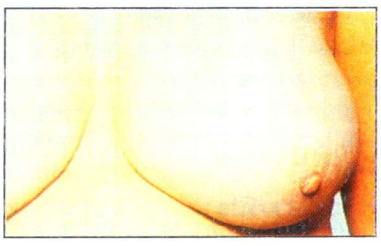
The findings of this study are depicted in table I-VIII (Sex, age, clinical stage, methods of diagnosis, histopathological types, treatment received primary response to treatment, years of survival respectively.

Table - I: Distribution of sex (N = 43)

Sex	Number of Patients	Percentage(%)
Female	42	97.68
Male	01	2.32



The relationship of carcinoma of the breast to the quadrants of the breast.



Paget's disease of the nipple

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5. **Dr. A.S.M. Jahangir Chowdhury,** MS (Ortho.), Asst. Professor, Orthopaedic Surgery Dept. FMCH, Faridpur.

Table-II Distribution of patient by Age (N=43)

Age group years	No of Patients	Percentage (%)
0-15	0	0
16-30	5	11.63
31-45	21	48.84
46-60	12	27.91
61-75	4	9.30
76-80	1	2.32
81-105	0	0
	Total=43	Total=100

Table-III Distribution of patient in clinical stage (N=43)

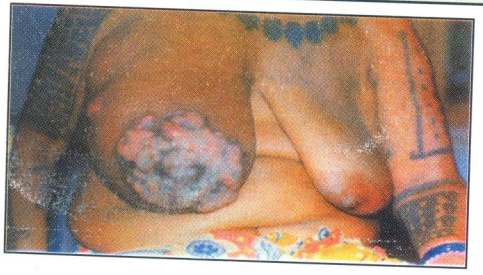
Clinical Stage	Number of patients	Percentage (%)
I	6	13.95
II	23	53.49
III	8	18.61
IV	6	13.95
	Total=43	Total=100

Table IV: Methods of diagnosis (in addition to clinical feature). (N = 43).

Method	No. of Patients	Percentage (%)
Biopsy & histo-pathology	36	83.72
FNAC	3	6.98
Clinical+Radio logical	49	30
	43	Total = 100

Table-V: Histopathological types. (N = 43)

Histopathogical Types.	No. of Patients	Percentage (%)
Infiltrating Ductal Carcinoma	34	79.07
Metastatic Adenocarcinoma	2	4.65
Medullary Carcinoma	2	4.65
Not done	3	6.98
Inconclusive	2	4.65



Enormous fungating carcinoma of right breast with enlarged axillary lumph nodes

Table VI Distribution of patients depending on treatment.

Treatment received	No.of Patients	Percentage(%)
Surgery + Chemotherapy (6 cycles)+Radiotherapy+ Hormonetherapy	17	39.54
Surgery + Chemotherapy (incomplete)+ Radiotherapy+ Hormonetherapy	5	11.63
Surgery+Chemotherapy (incomplete)	13	30.23
Surgery + only hormonetherapy	1	2.32
Only chemotherapy	5	11.63
Only supportive treatment	2	4.65

Table- VII Primary treatment response

Response	No. of Patients	Percentage (%)
No evidence of local or distant Metastasis.	30	69.77
Evidence of local Recurrence	4	9.30
Evidence of local + Distant metastasis	5	11.63
Evidence of distant Metastasis	4	9.30

Table VIII Distribution of patients depending on treatment.

Years of survival	No.of patients	Percentage(%)
One year	41	95.35
2.5 year	35	81.39
More than 5 years	2	4.65
Expired	08	18.61

Most of the affected patients were between 31 - 45 years (48.84%)

Discussion

Breast Cancer is the commonest form of malignancy in western countries and accounts for 12% of all cancers, 10% of all cancer deaths, 20-25% of all female cancer death. Response with treatment is not disappointing. Mortality from breast cancer exceeds that of the unaffected women even upto 30 years or more after initial treatment[6].

Methods of treatment for breast cancer are local/loco-regional or systemic. Local treatments are used to remove, destroy, or control the cancer cells in a specific area. Surgery and radiation therapy are local treatments. Systemic treatments are used to destroy or control cancer cells throughout the body. Chemotherapy and hormone therapy are systemic treatments. Different forms of treatment may be given at the same time or one after

another. Combination of above treatments can provide the hope of cure in early cases[7].

The addition of mastectomy to chemotherapy plus radiotherapy improved distant dieases and overall survival in patients with a clinical complete or partial response to induction chemotherapy.[8]

In our study, infiltrating ductal carcinoma, metastatic adenocarcinoma, medullary carcinoma were 97.07%, 4.65% and14.65% respectively. There observations are in agreement with the findings of A. Rouf and S. Shamin in our country[9] and of Berg and Huntter[10] in USA, where ductal carcinoma appeared to be 75.4% and lobular carcinoma 7.3% among all the malignant lesions. The results of treatment of carcinoma breast in our country is not highly appreciating due to very few radiotherapy center, late stage of diagnosis, poverty, lack of knowledge and ignorance. Effective treatment as well as prevention of cancer in not possible most of the time. Screening represents an alternative approach to try to reduce mortality from breast cancer[11]. Early detection of breast cancer is of vital importance for increasing survival rate and decreasing mortality rate in breast cancer.

In our study, after a median follow up of 21 mothers (Range, 12 - 30 months), over all survival were 9 months (range 13 - 30 months).

Conclusions

The CMF combination chemotherapy is safe and effective for a non adjuvant setting in breast cancer.

A longer follow-up is necessary for the end point results. 15 years follow up is suggested.

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(Continution of the case report from page No - 21)

was without jaundice and all other liver enzymes were within normal limit. Tropical eosinophilia, was not substantiated by clinical pictures, although patient was given diethylcarbamazine and steroid for moderately positive CFT for filaria and Addison's disease respectively.

Regarding, polycythaemia rubra vera, cold or acquagenic pruritus was not present and hematological picture did not correlate[3].

Addisonian like pigmentation is a broad category under which there are several diseases which can produce addison's disease like pigmentation. These are hyperthyroidism, lymphoma, pheochromocytoma, scleroderma, carcinoid, cushing's syndrome. ACTH producing tumour etc. Besides addison's disease all causes were excluded. Probably pruritus and pigmentation were secondary to adrenal insufficiency. Whether could it be due to any autoimmune or viral or bacterial cause!

Great dilemma was in diagnosis and management of this patient. Yet his life could not be saved. Simple pruritus can lead to devastating and life threatening consequence which should be dealt carefully, sincerely and sympathetically.

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Generalized Pruritus: Severity leading to suicide- A case report

Mir Nazrul Islam[1], Kamrul Ahsan[2], M Muzammal Haque[3], M Rafiqul Islam[4], Hasan M Khan[5]

A 15 years old young boy, barber by profession attended at BIRDEM skin OPD on last week of June, 2001 with intense generalized itching and gradual hyperpigmentation all over the body for more than 3 years. He had no drug allergy or any systemic disease without any family history of atopy or urticaria.

On examination, hyperpigmentation was more prominent on sun exposed areas with lichenification and excoriation on both extremities. Diffuse pigmentation was also observed on oral mucosa and palms with accentuation in the creases. He had acneform eruptions on face and shiny finger nails with linear hyperpigmentation. With all available investigations, he had mild eosinophilia with moderately positive CFT for filaria. He had very low serum cortisol with normal electrolytes. All other investigations like hematological, biochemical, immunological and radiological were within normal limit except raised alkaline phosphatase. His skin biopsy was non-specific. With consultation of endocrinologist he was managed with adequate amount of prednisolone, antihistamines, anxiolytic and emollient but without satisfactory improvement during his first follow up. He was advised for next follow up with short appointment. But after a month, his brother informed that he committed suicide due to prolonged therapeutic failure.

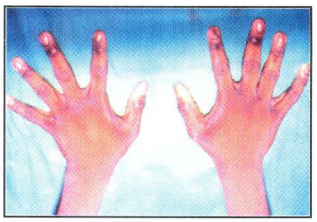

Fig-1. Hyperpigmented, hyperkeratotic and lichenified areas on the dorsum of hands with shiny nails.

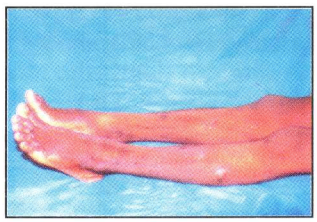

Fig-2. Lower extremities showing hyperkeratotic hyper pigmented lichenified areas with excoriation on the frontal aspect.

Fig,. 1,2,5 from Department of Dermatology, BIRDEM

Fig. 3 from Department of Dermatology Jahurul Islam Medical College Hospital

Fig. 4 from Department of Endocrinology, BIRDEM

Discussion

Pruritus (itch) is the predominant symptom of skin disease. It is defined as a sensation which elicits a desire to scratch. Itch and pain are received by unspecialized nerve endings located close to dermo-epidermal junction. Itch receptors are unmyelinated confined to skin and cornea.

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3. **Dr. Md. Muzammal Haque,** MBBS, DD (Thailand), Asst. Prof. Dept of Dermatology, Jahurul Islam Medical Collage and Hospital.
4. **Dr. Md. Rafiqul Islam,** MBBS, DEM (DU) Senior Medical Officer, Dept. of Endocrinology, BIRDEM, Dhaka.
5. **Prof. Hasan Mohd. Khan,** Honorary senior consultant, Dept. of Dermatology, BIRDEM, Dhaka.

Physical and chemical substances produce various types of itching, among which histamine is the main responsible chemical. Regarding etiology of pruritus, skin disorders, systemic diseases and some other miscellaneous factors are responsible[1].

Our patient initially had mild and localized pruritus with low intensity which gradually extended all over the body and became severe both physically and psychologically. Itching was his main concern rather pigmentation which affected his normal life. Provisionally we thought it could be chronic Actinic Dermatitis. Severe generalized pruritus due to systemic causes, Addisonian like pigmentation, primary biliary cirrhosis, Tropical eosinophilia and polycythaemia rubra vera. Though the patient was poor, we tried to do almost all available investigations, as complement from various corner. Almost all investigative parameters were within normal limit except eosinophil count (E-12%, TEC-1200) with moderate positive CFT for filaria. His serum cortisol level was low (basal level -113.4). Rapid ACTH stimulation test showed complete adrenal insufficiency.

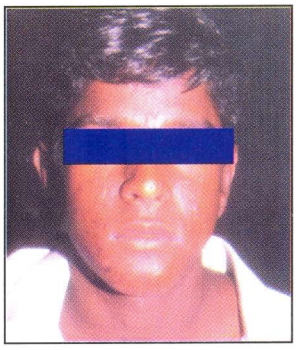

Fig-3. Acneform eruptions with hyperpigmentation on face and neck.

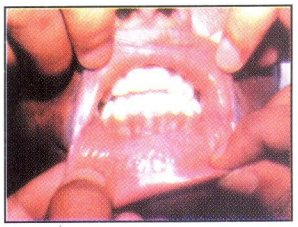

Fig-4. Diffuse hyperpigmented patches over buccal mucosa.

Beside this, his serum alkaline phosphatase level was raised. No correlation could be detected to G.I.T, hepatobiliary, and bone related disorders. Although liver biopsy was indicated, but could not be possible due to financial problem and post biopsy observation would not be possible as the patient was far from Dhaka, near Tripura border.

Special relevant investigations like concentration of Ceruloplasmin, serum ferritin, serum copper, viral markers, thyroid, renal and liver screening including ultrasonogram, endoscopy all were within normal limit.

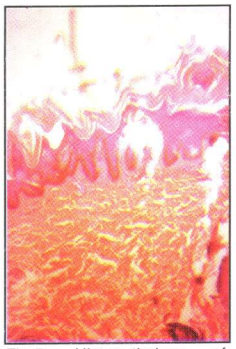

Fig-5. Histopathology of leasional skin biopsy showed hyperkeratosis and pigmentory changes in the basal layer.

History of this patient does not suggest chronic Actinic dermatitis[2], because of absence of photosensitive dermatitis spreading from localized to generalized pattern. Regarding Primary Biliary Cirrhosis, itching with raised serum alkaline phosphatase was in favour, but patient

(The rest of the case report is given on page No - 20)

Glucose Intolerance and Diabetes in Pregnancy : Screening and Diagnosis

Showkat Jahan[1], Sultana Jahan[2], M A Mannan[3]

Introduction

Diabetes mellitus is the most common metabolic disorder which complicates pregnancy[1]. Its incidence rate is about 1-3% majority of which develops during pregnancy (Gestational Diabetes Mellitus -GDM)[2]. Diabetes has significant implications on pregnancy and before the introduction of insulin, outcome of pregnancy was very poor. But in the recent years, there has been remarkable progress in the outcome of diabetic pregnancy due to meticulous glycaemic control and careful medical and obstetric management. Currently, the major challenges of caring for diabetes in pregnancy are to screen pregnant women adequately, to reduce the risk of congenital abnormalities, to achieve the best possible pregnancy outcome and to prevent immediate and long term consequences of the disease.

Diabetogenic effects of pregnancy

Pregnancy is considered to be a potentially diabetogenic state[1]. This is because of the secretion of anti-insulin factors such as HPL (Human placental lactogen) and cortisol which counter the peripheral action of insulin[1]. Serum levels of HPL rise from the 8th to the 32nd week of pregnancy (when the glucose haemostasis is at its worst), then flatten out until labour, disappear within a few hours of delivery[3]. Other hormones that contribute to insulin resistance include oestriol, progesterone and placental insulinase[2].

Screening

Screening means 'presumptive identification of unrecognised diseases by the application of diagnostic procedures which can be applied rapidly and safely[4].

Most patients with gestational diabetes are asymptomatic and detected biochemically. In view of the potential serious sequelae of diabetes in pregnancy, most authorities recommend a routine screening for detection of glucose intolerance during pregnancy[5,6].

The purpose of screening is to subject a minimum number of cases to the diagnostic test - the oral glucose tolerance test (OGTT) and to detect as many as possible cases[7].

Population to be screened

Whether all pregnant patients or the risk patients are to be screened is an area of controversy. At one time, the concept of potential diabetic was in need of a full OGTT to define pregnant woman. This concept is cost effective. In addition, screening on potential diabetics misses half the women with glucose intolerance in pregnancy. There is now a preference for screening the entire population using a simpler test[2,6].

Best time for screening

Ideally, screening should be performed at the initial visit in order to detect the rare previously undiagnosed cases of sub-clinical DM[7] this is particularly justifiable in patients with potential risk factors. If the first test is negative, the screening test is to be -repeated at 28 weeks of gestation[2, 5, 6, 7]. In patients lacking any risk factors screening is usually performed between 24 and 28 weeks[5].

Table -1.

Risk factors for glucose intolerance in pregnancy [2,6,7,8,9,10]

1. Diabetes in first degree or second degree relative
2. Obesity (Body mass index 30)
3. Age > 30 years
4. Past obstetric history shows -
   - (i) Unexplained intrauterine death/stillbirth or neonataldeath
   - (ii) Large baby (> 4 kg or 4.5 kg)
   - (iii) Congenital abnormality
   - (iv) Poor reproductive history (> 3 spontaneous abortion in 1st/2nd trimaster)
   - (v) Impaired glucose tolerance
5. Current pregnancy shows -
   - (i) Polyhydramnios
   - (ii) Macrosomia
6. Presence of significant glycosuria
7. Repeated moniliasis
8. Recurrent UTI

Using this screening method, approximately 15% of patients will have an abnormal screening test. Of those patients, who are then subjected to full OGTT, approximately 15% will be diagnosed as having gestational diabetes[5].

Screening test

A number of screening tests are available, but the 'gold standards' for screening for gestational diabetes is generally accepted as the 50 gm. oral glucose challenge test[8], sometimes called a mini glucose tolerance test[9].

The recommended test is determination of plasma glucose 1 hour after ingestion of 50 gm of glucose at any time of the day. The patient need not be fasting and no dietary preparation is required.

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If 1 hour plasma glucose is > 7.8 mmol / L (140 mg /dl) the patient should have a full OGTT [2,8].

If the level is > 11.1 mmol/ l (200 gm/dl) the patient should have a fasting glucose measurement[2].

If the fasting is frankly abnormal, 120 mg/dl or greater, the patent is diabetic and doesn't need a full OGTT[2].

This test has a sensitivity of 80% and a specifically of 90% [8] which is superior to any other screening test.

Diagnosis

The gold standard for diagnosing diabetes mellitus is by the oral glucose tolerance test (OGTT)[10]. However, different criteria using different glucose loads have been proposed for interpreting the OGTT during pregnancy.

The tests that are widely used -

Table -2

Upper limits of normal for 3 hour OGTT[2].

Venous plasma glucose value		
Fasting	96 mg/dl	5.3 mmol / l
One hour	172 mg/dl	9.6 mmol / l
Two hour	156 gm/dl	8.49 mmol / l
Three hour	131 mg/dl	7.31 mmol / l

3 Hour OGTT using 100 gm glucose challenge

or

2 hour OGTT using 75 gm glucose challenge (WHO) 3 hour OGTT

After adequate carbohydrate loading for 3 days (generally 150-200 g/day), the first step is a fasting plasma glucose sample. Thereafter, the patient consumes 100 gm of glucose and blood is drawn at 1, 2 and 3 hour thereafter for determination of plasma glucose levels.

The normal values are shown in table2.

If 2 or more of these values are abnormal, the patient has gestational diabetes[2]. One abnormal value is considered suspicious and there are risks of macrosomia and pre-eclampsia - eclampsia[11]. Patients with no abnormal value in 3 hour OGTT after an abnormal screening are at risk of macrosomia[12]. If the test is negative, but there is high suspicion of diabetes; it may be repeated at 30 -32 weeks[1].

2 hour OGTT (WHO)

In 2 hour OGTT recommended by WHO, diagnosis is based on fasting and 2 hour postglucose plasma / blood

Table -3

WHO criteria for diagnosis of IGT and DM [9, 10, 13]

Venous plasma (whole blood) level in mmol / l		
	IGT	Diabetes
Fasting	< 7.8 (6.7)	> 7.8 (6.7)
2 hour post glucose	7.8 -11.1 (6.7 -10)	> 11.1(10)

* Values in plasma is 10% greater than that of whole blood

values with 75 g of glucose and the diagnostic criteria has been defined[10].

Table -4

Modified WHO criteria for diagnosis of IGT and DM in pregnancy[8]

	Normal	IGT	DM
Fasting	< 6	6-7.9	>8
	or	and	and/or
2 hours	< 9	9-10.9	> 11.0

But, the WHO criteria were based on non pregnant women and there are well recognised changes in pregnancy particularly in the third trimester - a higher postprandial glucose concentrations and marginal decrease in fasting glucose concentrations[7]. Population studies in the third trimester suggest that about 10% of apparently normal women have impaired glucose tolerance (IGT) using the WHO definition[7]. So, a modified WHO criteria recommended by Hadden is now followed in some countries.

It is important to mention that GTT should be reserved for borderline cases only and a GTT is unnecessary when the fasting plasma glucose is >7.8 mmol / litre and /or when the 2 hour value is >11.1 mmol/litre[13].

Simultaneous blood and urine glucose measurements can be used to define a low renal threshold for glucose. Urinary glucose has been shown to be an unreliable method of detecting potential diabetes due to low renal threshold in pregnancy.

Summary

Screening for detection of IGT and DM should be universal at least at around 28 weeks of pregnancy[2, 6].

* Mini glucose tolerance test is the best for screening[8].

* OGTT is reserved for borderline cases, not for cases with frank diabetes[13].

Conclusion

Diabetic pregnancy remains an important medical disorder in pregnancy and is associated with higher incidence of pregnancy complications. As most of the

patients are gestational diabetics having no symptoms, diagnosis followed by screening is the essential part of better management.

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MSD NEWS

MSD personnel of Orion Laboratories Ltd. and Orion Infusion Ltd. spent a busy schedule in first quater of 2002, in arranging seminars in different venues as a part of Continued Medical Education Program.

Seminar at PABNA

A seminar jointly arranged by MSD, Orion Laboratories Ltd. and BMA, Pabna on (a) Childhood asthma and Neonatal resuscitation (b) Role of Zinc in Maternal and Child health was held on January 18, 2002 at Bandhan Community Centre, Pabna. The seminar was chaired by Prof. Md. Khalilur Rahman, Consultant, Chest disease clinic, Pabna and President BMA, Pabna. Dr. Shamsuddin Mondal, Civil Surgeon, Pabna and Dr. Sabirul Islam, President BPMPA, Pabna were chief guest and special guest respectively. Dr. Md. Mokhlesur Rohman , Pediatrician, South East Hospital, London and DR. ATM Azizur Rahman, Manager, MSD, Orion Laboratories Ltd. were the speakers of the seminar.

Seminar at BIRDEM

A seminar was jointly arranged by MSD, Orion Infusion Ltd. and Department of Surgery, BIRDEM on "Management of Post-operative Infection" on January 22,2002 at BIRDEM Auditorium, Dhaka. The seminar was chaired by Prof. Mirza Mazharul Islam, Chief consultant, Surgery, BIRDEM. Prof. Humayun Kabir Chowdhury, Head of the dept. of Surgery and Chief-MISC was the key-note speaker of the seminar.

Dr. ATM Azizur Rahman, Manager, Medical Services Department, welcomed the learned participants. Mr.Tawhidul Bashar, Sales Manager, OIL thanked the speakers and audience.

Seminar at Dhaka Club Ltd.

A scientific meeting was jointly arranged by MSD, Orion Infusion Ltd. and Society of Laparoscopic Surgeons of Bangladesh on February, 15, 2002 at Dhaka Club Ltd. The seminar was chaired by Prof. ANM Atai Rabbi, Chairman of the Society and Chairman of the Dept. of Surgery, BSMMU. Prof. Humayun Kabir Chowdhury, Head of the Dept. of Surgery and Chief-MISC conducted the meeting. Prof. Khademul Islam, Dept. of Surgery, SSMCH, Asst. Prof. Mazharul Haque Khan, Dept.of Surgery, BSMMU, Asst. Prof. AHM Tawhidul Alam, Dept.of Surgery, BSMMU, were the speakers of the seminar. Prof. Motiar Rahman, Dept of Surgery, DNMCH, Asst. Prof. Julfiqar Haider Chowdhury, Dept of Surgery, BSMMU, Asst. Prof. MA Wahab Khan Chowdhury participated in the discussion. Dr. ATM Azizur Rahman, Manager, Medical Services Department, thanked the participants.

Seminar at National Heart Foundation and Research Institute

MSD, Orion Laboratories Ltd. also arranged a seminar on (a) " Acute Coronary Syndrome" (b) Overview on Antioxidant on March, 21, 2002 at Seminar room, National Heart Foundation Hospital Dhaka. Brig.Prof. Abdul Malik (Retd.) and Prof. (Dr.) R.K Khandoker were the chairpersons of the seminar. Dr. Fazilatunnesa Malik, Senior Consultant cardiologist, National Heart Foundation Hospital and Dr. NAM Momenuzzaman, Senior consultant cardiologist, National Heart Foundation and Dr.ATM Azizur Rahman, Manager, MSD, Orion Laboratories Ltd. were the speakers of the seminar.

Launching of new products

We have recently introduced the following new products in the market.

1) Clognil (Clopidogrel)

Clognil (Clopidogrel) , a thienopyridine derivative antiplatelet drug , which is indicated for the treatment of myocardial infarction , stroke, peripheral vascular diseases, angina and recurrent ischemic events. Clognil is presented in the form of Tablet 75mg.

2) Ormin (Metformin Hydrochloride)

Ormin (Metformin Hydrochloride) is a dimethylbiguanide, orally active anti-diabetic agent. It is indicated in NIDDM as monotherapy, or as adjunct to diet. Ormin may be used concomitantly with a sulfonylurea when diet and Ormin or sulfonylurea alone do not result in adequate glycemic control. It may also be used as adjunct therapy in combination with insulin in IDDM. Ormin is presented in the form of Tablet 850mg.

3) Azalid (Azithromycin)

Azalid (Azithromycin), a semisynthetic azalide (a subclass of macrolide),is an antibiotic. It is indicated in the treatment of upper respiratory tract infections, skin and soft tissue infections, sexually transmitted diseases and odontogenic infections. Azalid is presented in the form of Capsule 250mg, Tablet 500mg and Powder for suspension (200mg/5ml).

4) Lopres (Atenolol)

Lopres (Atenolol) is a β_1 - selective adrenergic receptor antagonist. It is indicated for the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction and cardiomyopathy. It is presented in the form of Tablet 50mg.

Interpretation of Anti-streptolysin O(ASO) Titre and Erythrocyte Sedimentation rate (ESR), C-reactive protein (CRP) for the diagnosis of Rheumatic fever - A review article

Akhtarun Naher[1], Ruhul Amin Miah[2], Yasmin Jahan[3]

Summary

Rheumatic fever(RF) and Rheumatic heart diseases(RHD) are still major causes of morbidity and mortality in the developing world today. Diagnosis and prevention, particularly prophylaxis become more important as increased urbanization with greater population pressure and economic problems, increase the prevalence. According to the latest publication, major manifestations are carditis, polyarthritis ,chorea ,erythema marginatum and subcutaneous nodules .Minor manifestations include fever, arthralgia and laboratory findings of elevated erythrocyte sedimentation rate(ESR), C-reactive protein(CRP), antistreptolysin O titre(ASO Titre) and prolonged PR interval on ECG. For making a diagnosis of acute rheumatic fever, two major or one major and two minor manifestations must be accompanied by supporting evidence of antecedent group A Streptococcal infection in the form of positive throat culture or elevated or rising antistreptolysin titre(ASO Titre). Although non specific for rheumatic fever, ASO titre,ESR, CRP are the most commonly employed tests to determine acute phase response status.Selection of an appropriate test to detect acute phase response in Rheumatic fever is rather confusing. . Confusion in interpreting the results of these tests may arise that warrants a judicious selection of the appropriate test. Thus ,this paper highlights the interpretations of these three tests that are often used in the diagnosis of Rheumatic fever .

Keywords : Rheumatic fever, Antistreptolysin O Titre, C reactive protein,Erythrocyte sedimentation rate

Introduction

Rheumatic fever (RF) and Rheumatic heart disease (RHD) is an important cause of morbidity and mortality especially in the developing countries including Bangladesh[1-3]. An estimate of 1.5 million in the developed world compared to 30 million elsewhere suffer from ongoing heart disease, 70 % of which will end in premature at an average age of 35 years [1]. Children from the age of 5 years. to young adulthood are most frequently affected. Overcrowding, proverty and limited access to medical care are important factors in its transmission[2-3]. These multi-system disease triggered by infection with specific strains of group A Streptococci which contain antigens that cross react with human connective tissue, particularly heart valve glycoprotein[4]. It is a disease complex preceded by beta-hemolytic streptococcal infection of upper respiratory tract produces a vicious cycle of Rheumatic fever, Rheumatic heart disease to incapacitating chronic heart disease, as a result significant number of morbidity and mortality occur.

Table 1 Prevalence of rheumatic fever and rheumatic heart disease by region from school children[1]

WHO region	Prevalence per 1000 school children(range)
Africa	4.7(3.4-12.6)
America	1.5(0.1-7.9)
Eastern Mediterranean	4.4(0.9-10.2)
South East Asia	0.12(0.1-1.3)
Western Pacific	0.7(0.6-1.4)
All region	2.2(0.7-4.7)

Diagnosis

The diagnosis of rheumatic fever is based mainly on clinical ground with some supporting laboratory investigations. Modified Jones Criteria[3] remain the internationally agreed standard for diagnosis (Table 2). Two major or one major plus two minor criteria are required unless chorea or late onset Carditis are present- a presumptive diagnosis, can be made. Carditis is present in around 50% of cases[3]. Echocardiography is increasingly available worldwide and will have an important role in diagnosis and management of valve disease.

An elevated acute phase reactant has been considered as a minor manifestation of rheumatic fever. Erythrocyte sedimentation rate and C reactive protein are the most commonly employed test to determine acute phase response status[5-6]. The erythrocyte sedimentation rate is influenced by age, sex, anaemia of the subjects and temperature whereas C- reactive protein remains unaffected by these factors. However, the influence of age and sex on ESR becomes apparent after 20 years of age which is beyond the usual limit of rheumatic fever .C-reactive protein is a member of acute phase protein

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family .An increase in plasma concentration of C- reactive protein may be detected within 6-10 hours after tissue damage and as the inflammatory response subsides the plasma concentration falls with a half time of 48 hrs. So, the C-reactive protein level(normal value < 6 mg/ml) will monitor the onset of inflammation or its response to treatment[7]. C -reactive protein can be measured on a stored sample .On the other hand, an increase in ESR may not be seen until 24-48 hours after inflammation begins. Therefore, it is evident that ESR has poor quality control and no reproducibility. Despite these drawbacks, ESR is still widely used in developing countries because it is less expensive, easy to perform. But it had higher false positive rate[5]. A false positive test may complicate clinical decision making and facilitate over diagnosis which in turn would result in unnecessary anxiety of the patient and family and exposure to long term antibiotic prophylaxis.However,it has been recommended that a negative C-reactive protein may rule out rheumatic activity[8].If a patient presents with active manifestation (s), C-reactive protein may be the test of choice and should be measured as soon as possible. If the test is negative in a highly suggestive subject,erythrocyte sedimentation rate may be measured as a second test taking into account the severity of anaemia. Erythrocyte sedimentation rate should be preferred for inactive cases. C-reactive protein test should be preferred in fresh and active patients.

Table 2 Revised Jones Criteria[3]

Major criteria	Minor manifestations
Carditis	Fever
Polyarthritis	Arthralgia
Erythema marginatum	Previous rheumatic fever or rheumatic heart disease
Subcutaneous nodules	Raised acute phase reactants (ESR,CRP, Leukocytosis)
Chorea	Prolonged PR interval

Plus supporting evidence of previous streptococcal infection(Anti Streptolysin O Titre, Throat culture or Scarlet fever)

ESR= Erythrocyte sedimentation rate : CRP= C-reactive protein

Anti-Streptolysin O (ASO) serum titer in excess of 160-200 units is considered abnormally high and suggests either recent infection with Streptococci or persistently high antibody levels due to an earlier exposure in a hypersensitive person[8]. Previous records in Bangladesh revealed that 51.7% patients fulfilled the revised Jones criteria for diagnosis of rheumatic fever[9]. The remaining cases did not fulfill the Jones criteria for diagnosed as RF and were falsely diagnosed as RF or over diagnosis of RF and received prophylactic antibiotic as all of them had raised ASO titres. Only 2.5% patients presented with chorea. In another study, it was also revealed that the incidence of inappropriate diagnosis of RF was 64%. All of them were getting prophylactic penicillin for many years[10].

Conclusion RF and RHD is still major problem in developing countries.This paper conclude that no one test is ideal for the diagnosis of rheumatic fever but they are complementary depending on clinical situations. Clinicians of various disciplines dealing with such cases should be careful and judicious in diagnosis and prescribing prophylactic antibiotic for rheumatic fever. Due to over diagnosis of RF, physical and mental sufferings of the patients in addition to undue economic burden occur and that can be reduced by dissiminating adequate information or proper case diagnosis to the physician.

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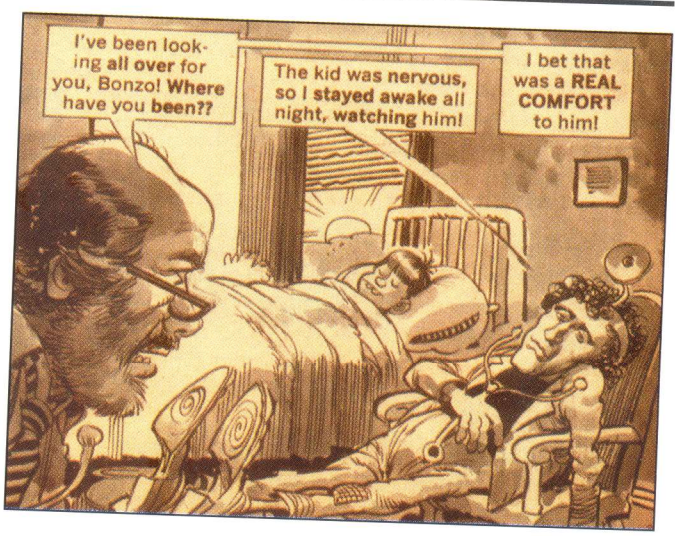

Antioxidants in Diseases and Health

M Matiur Rahman[1], M Motahar Hossain[2], MA Ahbab[3], M Ismail Patwary[4]

(This article is continued from the previous volume 11)

Antioxidants in disease:

a) Atherosclerosis and coronary artery disease

Atherosclerosis is a disease in which the oxidation hypothesis is the oxidation of low-density lipoprotein (LDL) has been suggested to be a key step in the initiation of the early atherosclerotic lesion the hall mark of which is macrophage cholesterol accumulation and foam cell formation.[16] Among the most well-characterized effects of LDL oxidation are increases in the expression of endothelial cell surface adhesion molecules that facilitate the mobilization and uptake of circulating inflammatory cells[17,18] and alterations in the chemotactic properties of monocytes and monocyte-derived macrophages[19,20] in a manner expected to increase their residence within the artery wall. Oxidation of the apolipoprotein B component alters LDL receptor recognition properties, leading to avid internalization of LDLs by macrophages via scavenger receptors,[21,22] a key step in the formation of macrophage-derived foam cells.

These concepts provide evidence that antioxidants may be potentially attractive therapeutic agents. Indeed, several lines of evidence suggest that antioxidants, especially alpha-tocopherol, have potential beneficial effects with regard to cardiovascular disease. In vitro, alpha-tocopherol has been shown to inhibit platelet adhesion and aggregation and smooth muscle cell proliferation, exert anti-inflammatory effects on monocytes, and improve endothelial function.[23] Also, supplementation with alpha-tocopherol has been shown to decrease lipid peroxidation, platelet aggregation, and proinflammatory activity of monocytes. Two prospective cohort studies by Stamper et al,24 (analyzing data from >85000 participants followed up for periods of 8 years) and Rimm et al, 25 (data from>39 000 male participants followed up for 4 years) described a substantial lowering of risk for vitamin E supplement users versus nonusers and an inverse relationship between risk and duration of supplement use. However, clinical trials with alpha-tocopherol supplementation to date have been equivocal. In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a randomized trial tested the effects of daily doses of 50 mg (50 IU) of vitamin E (all-racemic α tocopherol acetate), 20 mg of β-carotene, both, or placebo for 5 to 8 years in a population of>29 000 male smokers[26]. The major end point was lung cancer, but the investigators also evaluated coronary heart disease. No reduction in risk of lung cancer or major coronary events was observed with any of the treatments. Thus, although mounting in vitro evidence and animal models provide a sound scientific basis for alpha-tocopherol supplementation, further clinical trials are required before a definitive recommendation can be made with respect to the primary and secondary prevention of heart disease.[27] Several evidence suggests that the major effect, if any, is found at supplemental intake levels at or greater than 100 IU/d. Swain and Kaplan-Machlis recommend 400 IU or more per day of vitamin E to patients at high risk or already diagnosed with coronary artery disease.[28] If confirmed in further trials, the net benefit of vitamin E supplementation among populations with existing coronary disease may be substantial.[29]

The inverse relationship between dietary flavonoids consumption and cardiovascular diseases may be associated with the ability of flavonoids to attenuate LDL oxidation, macrophage foam cell formation and atherosclerosis. Flavonoids can reduce LDL lipid peroxidation by scavenging reactive oxygen/nitrogen species, chelation of transition metal ions and sparing of LDL- associated anioxidants.[30]

Evidence for a protective role of vitamin C in the prevention of cardiovascular disease is inconclusive. Two recent reports provide some new observations that vitamin C may play a role in preventing manifestations of existing coronary artery disease, rather than in limiting disease progression.[31] Although these results suffer from the limitations of observational studies, they provide impetus for further investigation.

Reactive oxygen species (ROS) are formed at an accelerated rate in post-ischaemic myocardium. Cardiac myocytes, endothelial cells, and infiltrating neutrophils contribute to this ROS production. While it remains uncertain whether ROS contribute to the pathogenesis of myocardial infarction, there is strong support for ROS as mediators of the reversible ventricular dysfunction (stunning) that often accompanies reperfusion of the ischaemic myocardium.[32] Recent studies have suggested that antioxidants may affect clinical outcomes of cardiovascular events. The Indian Experiment of Infarct Survival Study[33] demonstrated that infarct size (as assessed from plasma levels of cardiac enzymes and ECG changes) and angina and total cardiac events (within the study period) were significantly reduced in individuals receiving antioxidants in the post-MI period.

Another potential therapeutic role for antioxidants is in the reduction of restenosis after angioplasty. This role has been addressed in several recent trials.[34, 35, 36, 37] The results have not been unequivocal and more research is needed in this area.

It should be noted that the American Heart Association does not recommend the use of antioxidant vitamin supplements to reduce CAD[38].

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b) Cancer

The concept of chemoprevention, the use of agents to inhibit and reverse carcinogenesis, has great appeal. It is hypothesized that ROS may be critically involved in the etiology of malignant disease through their possible impact on protooncogenes and tumour suppressor genes. Additionally, empirical evidence suggests that ROS may also affect the balance between apoptosis and cellular proliferation.[39]

The Beta-Carotene and Retinol EfficacyTrial (CARET),[40] conducted in 18,000 high-risk smokers in the US, found that a combination of beta-carotene and retinol palmitate resulted in a 28% increase in the incidence of lung cancer. The ATBC trial utilizing alpha tocopherol and β -carotene, had similar findings for the group taking β-carotene.[26] These two trials have caused a rethinking of the use of natural compounds as chemoprevention agents. These agents should no longer be regarded as harmless, but as having potential toxicities.[41]

There has been convincing evidence that polyphenolic antioxidants present in tea afford protection against cancer risk in many animal-tumour bioassay systems.[42] The epidemiological studies, though inconclusive, have also suggested that the consumption of tea is associated with a lowered risk of cancer. Much of this work has been done on green tea; less is known about black tea. A growing body of research has demonstrated green tea polyphenols to be powerful antioxidants with anticarcinogenic properties. Klaunig et al recently demonstrated that, in both smokers and nonsmokers, green tea consumption decreased oxidative DNA damage, lipid peroxidation, and free radical generation.[43] Other studies have shown an inverse association between green tea consumption and cancer risk, supporting a possible chemopreventive effect of green tea.[44]

c) CNS diseases

Although basic research has revealed many mechanisms involved in the repair or elimination of damaged neurons, turning these mechanisms into clinically useful neuroprotective interventions is a slow process. However, meaningful neuroprotection and neurorescue may be attainable in the very near future. In the meantime, neuron damaging oxidative stress can be kept in check by insuring adequate dietary sources of antioxidants. Although there is as yet little or no scientific evidence that dietary antioxidants are neuroprotective, the consumption of high antioxidant foods, such as blueperries and strawberries, is appealing to most people regardless of any neuroprotective potential.[45]

Stroke

In a recene prospective observational study, Vitamins C and E and β-carotene did not elicit protective effects on stroke risk.[46] Nevertheless, these nutrients may be important modulators of the outcome after the occurrence of a stroke. At present, optimal control of the classic stroke risk factors in combination with increased consumption of fruits, vegetables, and antioxidant nutrients may represent the safest and most efficient strategy to control stroke risk.[47]

Alzheimer's disease (AD)

Recent evidence in the field of AD research has highlighted the importance of oxidative processes In its pathogenesis.Examination of cellular changes show that oxidative stress is an event that precedes the appearance of neurofibrillary tangles, one of the hallmark pathologies of the disease. Although it is still unclear what the initial source of the oxidative stress is in AD, it is likely that the process is highly dependent on the presence of redox-active transition metals, such as iron and copper.[48] Many free radical scavengers (eg, vitamin E, selegeline, and Ginkgo biloba extract EGb 761) have produced promising results in relation to AD, as has desferrioxamine Iron -chelating agent -and anti inflammatory drugs and estrogens, which also have an antioxidant effect.[49,50]

Parkinson's and Huntington's disease

Antioxidants promise as potential therapies in the treatment of this disorders as oxidative stress plays an important role in causing the neurodegeneration associated with them.[51]

Motor neuron disease

Mutations of one of the superoxide dismutase genes are found in patients with familial amyotrophic lateral sclerosis (FALS), a progressive and fatal paralytic disease that is caused by the death of motor neurons in cortex, brainstem and spinal cord. Mutation converts a protective, antioxidant enzyme into a destructive, prooxidant form that catalyses free radical damage to which motor neurons are selectively vulnerable. Recent studies of neuroprotective agents in the FALS model show that inhibition of oxidative mechanisms (copper chelation therapy, dietary antioxidants, and coexpression of bcl -2) delays disease onset though it does not extend disease duration.[52]

d) Gastroenterological disease

Several epidemiological studies have demonstrated a close association between Helicobacter pylori infection and carcinoma of the mid or distal stomach. The increased levels of oxidative DNA damage, increased occurrences of apoptosis, and increased expressions of inducible nitric oxide synthase (iNOS) seem to provide the mechanistic links between H. Pylori infection and gastric carcinogenesis.[53] Rebamipide is the first anti- gastric ulcer and antigastritis drug that not only increases endogenous prostaglandin in gastric mucosa but also scavenges oxygen-derived free radicals and inhibits their production.[54]

e) COPD

The presence of oxidative stress has important consequences for the pathogenesis of COPD and Asthma. These include oxidative inactivation of antiproteinases, airspace epithelial injury, increased sequestration of neutrophils in the pulmonary microvasculature and gene expression of proinflammatory mediators. The sources of the increased oxidative stress in patients with COPD are derived from the increased burden of oxidants presents in cigarette smoke, or from the increased amounts of reactive oxygen species released from leukocytes, both in the airspaces and in the blood. Antioxidant depletion or deficiency in antioxidants may contribute to oxidative stress. The development of airflow limitation is related to dietary deficiency of antioxidants, and hence dietary supplementation may be a beneficial therapeutic intervention in this condition.[55]

The effect of diet in determining the etiology and clinical severity of asthma is uncertain. Epidemiologic studies suggest that antioxidants may have an important role in etiology of asthma and recent reports indicate that antioxidants may be beneficial in the prevention and treatment of the disorder.[56] The epidemiological evidence for a beneficial effect on

indicators of asthma and COPD of eating fish, fruit and vegetables in increasing. However, the effectiveness of dietary supplementation in open-population sample is often not demonstrated.[57] Recent research indicates that anti-oxidant treatment might be relatively more effective among those COPD Patients who respond less well to inhales steroids (low reversibility and heavy smoking).[58]

f) Cataract

While many experimental studies have shown a protective effect of vitamin C in age- related cataract. Oxidative damage in the lens can be prevented by vitamin C. However, a pro-oxidant effect of vitamin C through H_2O_2 generation has been suggested. Vitamin C has also been shown to play a role in protein glycation, which is observed in cataract formation. A protective effect of dietary energy restriction appears to be inversely related to plasma vitamin C levels in rodents. Moreover conclusions from human epidemiological and intervention studies are not uniform. The available evidence suggests that maintenance of sufficient plasma vitamin C is needed to prevent oxidative damage in the lens.[59,60] More over combination of vitamin C and E is effective in prevention of cataract.

g) Aging

The oxidative stress theory of aging is well supported by accumulated evidence from various aging intervention studies.[61] New evidence on the physiological roles of antioxidants, in addition to their well known role as free radical scavengers, is emerging from recent research. For instance, the beneficial effect of vitamin E in improving glucose transport and the insulin sensitivity and its putative role as a regulator of cell proliferation has opened new research dimension.[62] Proof that anti oxidants are beneficial is mainly limited to the demonstration that they do increase average life span, principally through a reduction in the incidence of life-threatening diseases in animals, but there is little current evidence to support an increase in maximum life span.[63]

Antioxidants in healthy people

Oxidative damage to biological structures has been implicated in the pathphysiology of cardiovascular disease and cancer, the 2 most common causes of death in developed countries. This has stimulated interest in the possible role of natural antioxidant vitamins in preventing the development of these diseases. Epidemiological studies have shown that high blood concentrations or dietary intake of antioxidant vitamins may have a protective effect. On the basis of these findings and powerful marketing strategies, many healthy members of the population are now voluntarily consuming antioxidant supplements. A number of long term, prospective, randomised, placebo- controlled trials examining the protective effect of antioxidant supplements have now been completed. Their results have been generally disappointing and have provided little evidence of efficacy. Of greater concern that antioxidants, notably betacarotene, might increase the rate of development of cancers in high risk individuals. For this reason regular consumption of antioxidant vitamins supplements without betacarotene cannot yet be advocated as a healthy lifestyle trait.[64]

Conclusion

In this review, we have examined the scientific evidence that supplementation with vitamin C, vitamin E, or β- carotene lowers in vivo oxidative damage to lipids, proteins or DNA based on the measurement of oxidative biomarkers, not disease outcome. With the only exception of supplemental vitamin E, and possibly with vitamin C, being able to significantly lower lipid oxidative damage in both smokers and nonsmokers, the current evidence is insufficient to conclude that antioxidant vitamin supplementation materially reduces oxidative damage in humans.[65] The most prudent and scientifically supportable recommendation for the general population is to consume a balanced diet with emphasis on antioxidant -rich fruits and vegetables and whole grains. Although diet alone may not provide the levels of vitamin E intake that have been associated with the lowest risk of coronary artery disease in a few observations studies[24,25] . In the case of secondary prevention, however, the results from clinical trials of vitamin E have been encouraging and if further studies confirm these findings, consideration of the merits of vitamin E supplementation in individuals with cardiovascular disease would be informed. Tea, however, can be an important source of what has been referred to as "non-nutrient" antioxidant phytochemicals.[67]

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Medi News

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Endometriosis-infertility link explained?

Infertility in women with mild endometriosis may be explained, at least in part, by a lack of certain proteins in the peritoneal fluid, says Robert Lessey (University of North Carolina, Chapel Hill, NC, USA). "Doctors like to lump everyone together, but not everyone with endometriosis is the same. Now we have a marker which may help identify those women who really need therapy."

Lessey and co-workers injected peritoneal fluid from women with and without mild endometriosis into recently mated mice around the time of embryo implantation. Mice given fluid from infertile women with endometriosis had fewer implantations than did mice receiving fluid from fertile women or from women with recently treated endometriosis; they also had reduced uterine concentrations of leukaemia inhibitory factor and did not express alphavbeta3 integrin. Embryo implantations may have been adversely affected by the infertile women's peritoneal fluid, suggest the authors (Fertil Steril 2000; 74: 41-48).

Because about half of women with mild endometriosis have no problem getting pregnant, a link with infertility is controversial, explains Lessey. "Those who don't get pregnant are given the diagnosis of 'unexplained infertility'. Yet they seem to have biochemical evidence that something is different, and these proteins are part of that difference." Thus, he insists, the absence of alphavbeta3 and reduced leukaemia inhibitory factor " could discriminate those women with serious defects" which really do interfere with implantation. Such women could be treated with surgical (lasers) or medical (gonadotrophin-releasing hormone) techniques to improve their chances of conceiving, he says.

A US company has started marketing a test of uterine receptivity based on these markers, notes Lessey. But although the test detects women missing alphavbeta3, its use is "premature", he says, since some women without alphavbeta3 are fertile. "Combinations of markers might be more specific."

"There are lots of factors out there", affirms Bryan Cowan, spokesperson for the American Society of Reproductive Medicine. " They affect sperm function, macrophage activation, peritoneal and tubal responses. So much is going on, and just about everything that's been tested shows differences, so this is unlikely to be the final kink." In addition, "the peritoneal fluid is outside of the uterus, and the endometrium being tested is on the inside. We have a big leap to demonstrate that the stuff on the outside of the uterus can actually influence the endometrium", he concludes.

Low oestrogen bad for brain cells

The cognitive decline that often accompanies old age or degenerative diseases such as Parkinson's disease could be caused, in part, by a lack of oestrogen, suggests a new study. "Oestrogen seems to exert a potent protective effect that maintains the integrity of the nigraldopamine system", says senior author Eugene Redmond (Yale University, New Haven, CT, USA). "When levels are low, key cells start to die", he adds.

Redmond's group measured the density of dopamine-producing neutrons in the compact zone of the substantial nigra in seven groups, each containing three African-green monkeys. Normal females had significantly more mesencephalic dopamine producing cells than males. When both ovaries had been removed, the number of dopamine cells in the substantial nigra of female monkeys decreased by more than 30% when measured at day 10 or day 30; this reduction could be reversed by oestrogen treatment started at day 1 or day 10. Treatment that began on day 30 did not prevent dopamine cell loss (F Neurosci 2000 20: 8604-09)

"This study provides an explanation for the large body of epidemiological data that shows that men suffer from Parkinson's disease more often than women", says Redmond. He adds that it also explains why women become more prone to the disease after menopause. "This study is very provocative: it extends the growing awareness that hormones can have powerful and selective effects on brain cell survival" says Bruce Ransom, Professor of Neurology at the University of Washington (Seattle, WA, USA). Unfortunately, he adds, "the article does not mention if oestrogen-deprived monkeys developed Parkinsonian features or greater sensitivity to MPTP-induced Parkinsonism. This information would greatly strengthen the hypothesis that oestrogen level affects the course of Parkinson's disease." Redmond agrees and confirms that longer term animal studies are already being planned.

If oestrogen treatment is to be of substantial benefit in Parkinson's disease, therapy would need to begin early if its neuroprotective effect were to have any clinical benefit. One possibility is to use imaging technology to detect the level of the dopamine transporter ligand present in the brain to detect early signs of dopamine deficit. "We are currently collaborating with colleagues in this field to see if we can identify people who might benefit from protective oestrogen, before they show obvious cognitive decline", he reports.

Under prescription blocks benefits of β-blockade

Proper use of β-blockers after myocardial infarction (MI) could make impressive health gains while potentially being cost-savings, according to a simulation exercise reported this week by US researchers.

Doctors are often wary of prescribing β-blockers after MI, but the economic consequences have not been rigorously examined, says first author Kathryn Phillips (University of California, San Francisco, CA, USA). To examine this "bigger picture", the team used the extensively validated Coronary Heart Disease Policy Model to project the effects of increasing post-MI β-blockade from current to target levels. A key reason for underprescribing is "the concern about β-blocker use in individuals with relative contraindications", says Phillips. But a 1998 report from the US National Cooperative Cardiovascular Project suggests that patients who were previously thought ineligible "can indeed benefit with little risk", she explains. The team therefore considered the effects of extending prescription of β-blockers to include those with relative contraindications.

The team projected that appropriate treatment with β-blockers for all eligible MI survivors in the year 2000 (about 92% of patients) would save 45 000 life-years, reduce deaths from coronary heart disease by 4300, and prevent 3500 further MIs, if continued until 2020. If annual cohorts were treated successively over 20 years, the cost-saving would be US$18 million, with 447 000 life-years gained. Treatment would potentially be cost-saving if increased prescribing was sustained over time, if β-blockers were taken for only 6 years,

or if the cost of β-blockers was less than $300 a year. If treatment was restricted to those without any contraindication, the epidemiological impact of increased prescribing would be reduced by about 60%. However, the authors conclude that "even if use were increased in only ideal patients, the benefits would be substantial" (JAMA 2000; 284; 2748-54).

Underprescription of β-blockers is so frequent that it is used as a quality measure in the most common managed-care performance measurement tool. This inclusion might have increased appropriate prescribing but reported use still falls short of target levels, indicating the efforts to date may have "plucked the low-lying fruit",. say the authors. Phillips advocates that "future studies should examine more closely the actual use of β-blockers in clinical practice, including the influence of patient preferences on provider prescribing". Consumer awareness of β-blockers side-effects, such as sexual dysfunction, and extensive marketing strategies by manufactures of alternative drugs, for example, calcium-channel antagonists, may have some influence on US patient preference, the adds.

Hope for prevention of mother-to-child transmission of HIV

The late breakers session on the last day of the XIIIth International AIDS Conference in Durban, South Africa (July 9-14) offered great hope for the beleaguered African nations in the prevention of HIV infection. Investigation of trials in several countries reported success with simple, cheap regimens of nevirapine given to mothers and newborn infants.

Results from the South African Intrapartum Nevirapine Trial (SAINT) confirmed that nevirapine is safe and effective at reducing mother-to-child transmission of HIV. Further, preliminary findings of long-term follow-up of the HIVNET-012 trial in Uganda (see Lancet 1999; 354: 795-802) showed that the benefits of this drug (42% reduction in relative risk versus zidovudine) are maintained at 18 months.

Worryingly, however, the investigators of the PETRA study (placebo-controlled trial of zidovudine and lamivudine combination regimens) reported that infection and mortality rates (of 21-26%) at 18 months in the various groups did not differ from those for placebo. Notably, breast-feeding rates were high -69% overall and as much as 99% in east Africa. The trialists attributed the loss of efficacy to "a high number of HIV-1 infections in breast-fed children", with breast-feeding doubling the risk of infection at 18 months. Additionally, the SAINT investigators recorded a seven-fold increase in HIV infection at 4-8 weeks in breasted infants.

Anna Coutsoudis (University of Natal, South Africa) presented the completed 15 month results of a vitamin A intervention trial in South Africa (see Lancet 1999; 354: 471-76). Most mothers (72%) chose to breastfeed, despite counselling about the associated risk of HIV transmission. Socioeconomic status was an important factor in this decision. Coutsoudis explained that the culture of breastfeeding, especially in sub-Saharan countries, was to introduce sugar water and cereals at about 6 weeks (mixed breastfeeding). At 15 months' follow-up, infection rates were high in babies who were mixed fed (26%), but remained lower in those exclusively breastfed for 3-6 months (19%). She suggested that adding other foods into the child's diet at this early stage introduces allergents or contaminant's to the gut, which in turn lead to an inflammatory response. The resulting damage to the gut might allow the virus to enter the baby's system.

Clearly, breastfeeding is a major factor in transmission from mother to child in African countries. But treatment substantially reduces transmission. Nevertheless, in South Africa, the Department of Health is hesitating about introducing nevirapine: "We are encouraged by the benefits that intrapartum nevirapine seems to offer .. we note, however, that more work is needed to confirm safety and efficacy ... particularly as regards the development of resistance".

Gene therapy holds promise for treatment of diabetes

Two new animal studies suggest that delivery of insulin genes using gene therapy may be better able to mimic the endogenous secretion profiles of insulin from pancreatic β-cells than conventional pharmacological approaches.

The long term aim of both research groups is to replace insulin secretion in patients with diabetes, though the two team took very different approaches to try to match insulin release with blood glucose concentrations. In the first study, Ji-Won Yoon (University of Calgary, Alberta, Canada) and colleagues inserted the DNA coding for a genetically engineered insulin analogue into an adeno-associated virus, and put the entire DNA construct under the control of the promotor region of the L- type Pyruvate kinase gene found in liver cells. When they injected the virus through the portal vein of either rates made diabetic by injections of the β - cell toxin streptozotocin of autoimmune diabetic mice, they found that the viral genome become incorporated exclusively in the liver cells and secreted the insulin analogue in to the animals' bloodstream for up to 8 month (Nature 2000; 408; 483-88).

"A gene therapy approach must be able to modulate insulin delivery over time", notes Jerrold Olefsky (University of California, San Diego, La Jolla, CA, USA), the author of a commentary that accompanies the paper. "Placing insulin secretion under the control glucose is nature's way of overcoming this problem, and the author's use of a glucose responsive promotor in the viral vector is a definite step forward, The paper represents a good example of how basic research can be applied to problems of clinical significance."

David Matthews(Oxford Center for diabetes, Endocrinology and Metabolism, UK) is also impressed by this approach : " This is clearly some way off being used in main, but it is a promising avenue using subtle methodologies. That it can reverse diabetes in a variety of rodents is, of itself, an outstanding achievement. As usual with science, we await the demonstration that such methods will work in the long term and be safe."

In the second study, Timothy Kieffer (University Alberta, Edmonton, Canada) and Co-workers opted for a different approach to obtain insulin secretion in response to meals. "We targeted naturally existing meal- responsive endocrine cells for insulin replacement", explains Kieffer. The cells in question, K- cells, are located predominately in the upper gastrointestinal tract and secrete the hormone glucose-dependent insulinotropic polypeptide (GIP) immediately after a meal . Indeed, the secretion patterns of GIP and insulin in humans can be virtually superimposed , since GIP normally acts as an anticipatory signal to β-cells that a meal Containing glucose is being absorbed from the gut.

"Our rational was that if we could engineer these k- Cells to produce insulin, it should be made and stored in the cells in advance, ready to be released promptly in response to ingestion of a meal", says Kieffer. With this in mind, the Researches created a strain of transgenic mouse which releases human insulin from K-Cells in the duodenum and stomach. Unlike control animals this mice did not develop diabetes after treatment with streptozotocin (Science 2000; 290: 1959-62). "We are now faced with developing a suitable delivery system to target this cells in the gut", Points out Kieffer.

Information for Authors

THE FOLLOWINGS ARE THE MINIMUM REQUIREMENTS FOR MANUSCRIPTS SUBMITTED FOR PUBLICATION

The **MANUSCRIPT** should be prepared according the modified Vancouver style as proposed by the International Committee of Medical Journal Editors (ICMJE). The entire uniform requirements document was revised in 1997 which is available in the Journal of American Medical Association (JAMA. 1997; 277:927-934) and is also available at the JAMA website. Sections were updated in May 1999 and May 2000. A major revision is scheduled for 2001. The following section is based mostly on May 2000 update.

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In **METHODS**, describe your selection of the observational or experimental subjects (patients or laboratory animals, including controls) clearly. Identify the age, sex, and other important characteristics of the subjects. Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations. Precisely identify all drugs and chemicals used, including generic name, dose, and route of administration. Reports of randomized clinical trials should presents information on all major study elements including the protocol (study population, interventions or exposures, outcomes, and the rationale for statistical analysis), assignment of interventions (methods of randomization, concealment of allocation to treatment groups), and the method of masking (blinding). Authors submitting review manuscripts are advised to include a section describing the methods used for locating, selecting, extracting, and synthesizing data.

In **RESULTS** section, when data are summarized, specify the statistical methods used to analyze them. Present your results in a logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations. Restrict tables and figures to those needed to explain the argument of the paper and to assess its support. Use graphs as an alterative to tables with many entries; do not duplicate data in graphs and tables. Number tables consecutively in the order of their first citation in the text, and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Identify statistical measures of variations such as standard deviation and standard error of the mean. Do not use internal horizontal and vertical rules. Be sure that each table is cited in the text. Figures should be professionally drawn and photographed. Supply raw data in separate page so that the figures may be redrawn. For x-ray films, and other material, send sharp, glossy, black-and-white photographic prints, usually 127 x 173 mm (5 x 7 in) but no larger than 203 x 254 mm (8 x 10 in).

In **DISCUSSION,** emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other material given in the Introduction or the Results section. Include in the Discussion section the implications of the findings and their limitations, including implications for future research. Relate the observations to other relevant studies.

Link the **CONCLUSIONS** with the goals of the study, but avoid unqualified statements and conclusions not completely supported by the data. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

ACKNOWLEDGMENTS may go as an appendix to the text, one or more statements may specify (i) contributions that need acknowledging but do not justify authorship, such as general support by a departmental chair; (ii) acknowledgments of technical help; (iii) acknowledgments of financial and material support, which should specify the nature of the support.

REFERENCES should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure.

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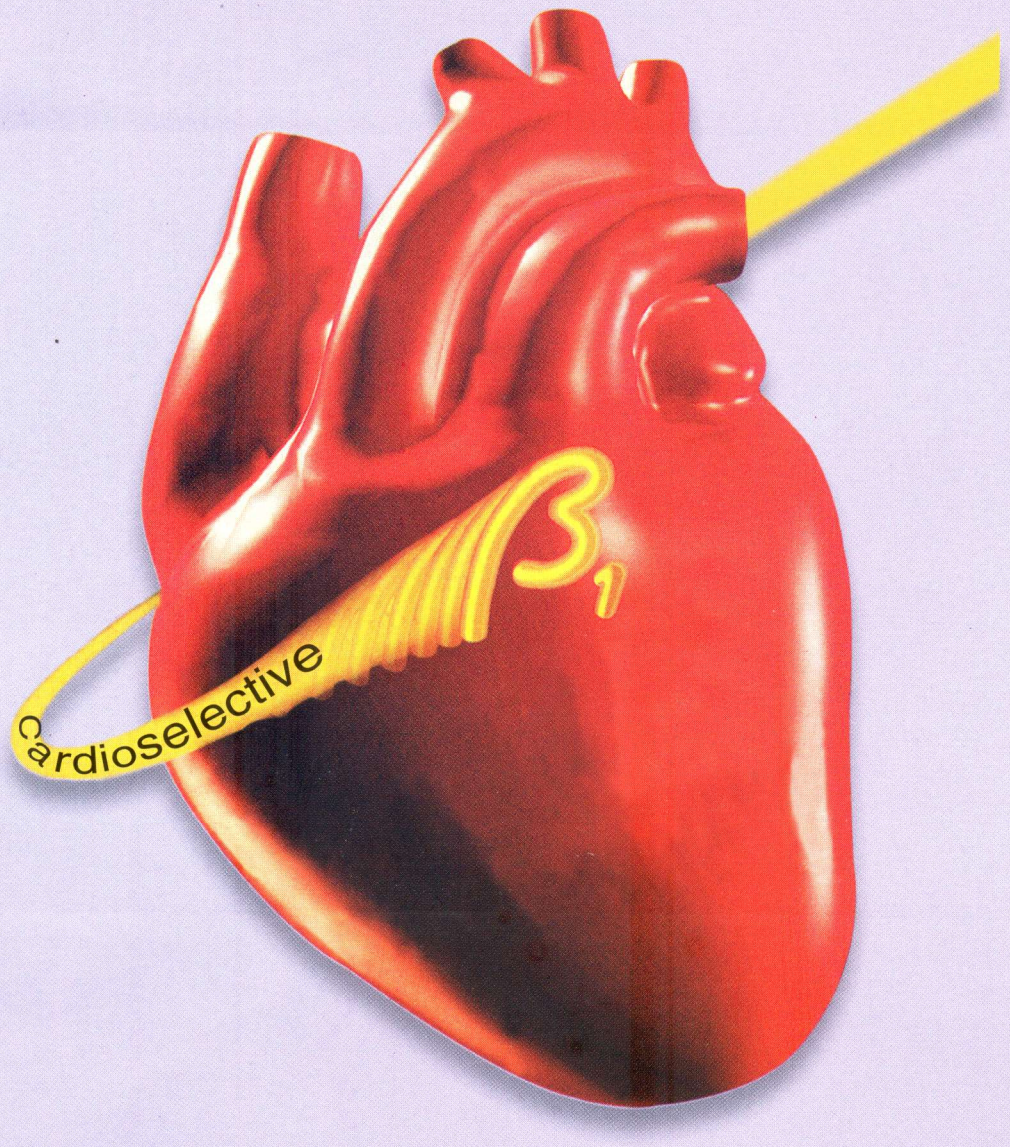

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