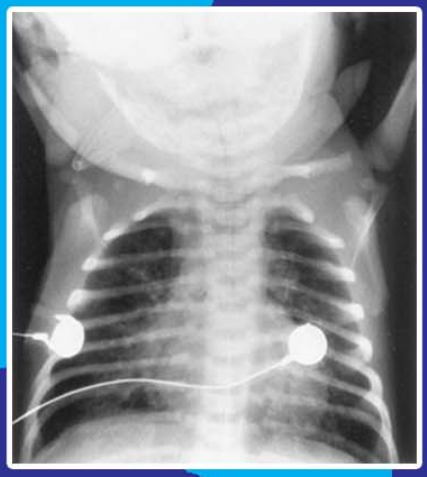
OCTOBER 2004 VOL 12 NO 3 ISSN 1681-5552

the SQUARE

healthcare bulletin



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OCTOBER 2004 VOL 12 NO 3

IN THIS ISSUE:

"the SQUARE"

From the Desk of Managing Editor

Dear Doctor:

Welcome to this edition of "*the SQUARE*"!

At first we thank you for your momentous reply! Those inspiring remarks really motivate us to produce more enlightening and interesting articles in all the future issues of "*the SQUARE*".

In this issue we highlighted features like "Chest Pain", the symptom that gives a serious concern to the sufferer! As "Chest pain" is very vast to describe, we condensed the best-published material on this topic focusing only the essentials. We have also focused on "Meconium Aspiration Syndrome", the incidence of which is thought to be higher in the developing countries and is associated with a greater mortality rate in the newborn.

In addition, we emphasized on the essentials of "Fever", a very common symptom encountered by everyone. We also have a special feature on "Hyperthyroidism-Graves' Disease" in this issue.

Besides, we have our regular feature on "Product profile", "Medical Breakthrough" and, "*SQUARE* in International Business".

Every effort has been made to make this issue interesting and we are quite sure that you will enjoy this issue as well.

On behalf of the management of *SQUARE*, wishing you all a very healthy, happy and prosperous life.

Omar Akramur Rab

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Chest Pain

Chest pain (chest tightness or pressure, chest discomfort) is a common symptom, which can be caused by many different conditions. There are many possible causes of chest pain. Some causes are mildly inconvenient, while other causes are serious, even life threatening.

Causes

Chest pain has many possible causes, all of which deserve medical attention. The causes of chest pain fall into two major categories - cardiac and non-cardiac causes.

Cardiac causes

- ❑ Myocardial infarction
- ❑ Myocardial ischemia (angina)
- ❑ Pericarditis
- ❑ Myocarditis
- ❑ Mitral valve prolapsed syndrome
- ❑ Pericardial effusion
- ❑ Heart tamponade
- ❑ Arrhythmias
- ❑ Aortic aneurysm
- ❑ Dissection aortic aneurysm
- ❑ Ruptured aortic aneurysm

Non-Cardiac causes

- ❑ Emotional conditions
  - ● Anxiety attack
  - ● Panic attack
  - ● Stress
- ❑ Digestive system conditions
  - ● Heartburn
  - ● Hiatus hernia
  - ● GERD
  - ● Esophagitis
  - ● Gallbladder disease
  - ● Pancreatitis
- ❑ Lung conditions
  - ● Pleuritic chest pain
  - ● Hyperventilation
  - ● Pneumonia
  - ● Chest infection
  - ● Pleurisy
  - ● Pulmonary embolism
  - ● Pneumothorax
  - ● Collapsed lung
  - ● Diaphragm irritation
  - ● Lung cancer
  - ● Connective tissue disease
  - ● Systemic lupus erythematosus (SLE)
  - ● Pleural tumor
  - ● Diaphragm disorder

Chest muscles disorders or bone disorders

- ❑ Bruised/broken rib
- ❑ Rib injury
- ❑ Chest cartilage disorder
- ❑ Chest muscle pain/spasm
- ❑ Intercostal muscle sprain
- ❑ Coxsackie B virus
- ❑ Spinal arthritis
- ❑ Spinal disc disease
- ❑ Costochondritis
- ❑ Nerve conditions
  - ● Shingles
  - ● Chest nerve irritation
  - ● Nerve root compression

Medications or substances causing Chest pain

- ● Caffeine
- ● Alcohol
- ● Smoking

Some possible causes of sudden chest pain include

- ❑ Heart attack or acute myocardial infarction
- ❑ Angina- first episode might be classed as "sudden"
- ❑ Anxiety attack
- ❑ Panic attack
- ❑ Esophagitis
- ❑ Pneumothorax
- ❑ Chest nerve irritation
- ❑ Pulmonary embolism
- ❑ Dissecting aortic aneurysm
- ❑ Pericarditis
- ❑ Pancreatitis

Some possible causes of recurring chest pain include

- ❑ Heart attack
- ❑ Angina
- ❑ Hiatus hernia
- ❑ Lung disease
- ❑ Chest infection
- ❑ Lung cancer
- ❑ Gallbladder disease
- ❑ Arrhythmias
- ❑ Aortic aneurysm
- ❑ Pericarditis
- ❑ Aortic valve disorder
- ❑ Chondritis

Chest Pain in Children and Adolescents

Chest pain in children, and especially adolescent is fairly common and is mostly benign and self-limited.

Differential Diagnosis of Chest Pain in Children

Cardiac Diseases

Cardiac disease is a rare cause of chest pain in children. However, myocardial infarction can rarely result from anomalous coronary arteries, and there may be no warning of this condition. Some children will have a pansystolic, continuous, or mitral regurgitation murmur or gallop rhythm.

Arrhythmias may cause palpitations or abnormalities on cardiac examination in some children. Supraventricular tachycardia is the most common arrhythmia, but premature ventricular beats or tachycardia also can cause episodes of brief, sharp chest pain.

Hypertrophic obstructive cardiomyopathy is an autosomal dominant structural disorder; therefore, there often is a family history of the condition. Children may have a murmur that may be audible.

Person suffering from chest pain

Mitral valve prolapse may cause chest pain secondary to papillary muscle or endocardial ischemia.

Pericarditis presents with sharp, stabbing pain that improves when the patient sits up and leans forward. The child usually is febrile; is in respiratory distress; and has a friction rub, distant heart sounds, neck vein distention, and pulsus paradoxus.

Myocarditis presents as mild pain that has been present for several days. After a few days of fever, vomiting and lightheadedness, the patient may develop pain or shortness of breath on exertion. Examination may reveal muffled heart sounds, fever, a gallop rhythm, or tachycardia. The patient also may have orthostatic changes.

Musculoskeletal Pain

This is one of the most common diagnoses in children who have chest discomfort.

Trauma to the chest may result in a mild contusion or a rib fracture.

Costochondritis is common in children, and it is characterized by tenderness over the costochondral junctions with palpation.

Respiratory Conditions

Severe cough, asthma, or pneumonia may cause chest pain because of overuse of chest wall muscles.

Exercise-induced asthma may cause chest pain.

Spontaneous pneumothorax.

Some causes of chest pain require prompt medical attention, such as angina, heart attack, or tearing of the aorta. Other causes of chest pain can be evaluated electively such as spasm of the esophagus, gallbladder attack, or inflammation of the chest wall. Therefore, an accurate diagnosis is important in providing proper treatment to patients with chest pain. The patient's history is crucial and careful empathetic communication with both the patient and relatives is important.

Obtaining the Chest Pain History

Most of the important decisions are made based on the history of the chest pain. When physical findings and lab tests are non-specific, as they often are in chest pain patients, the history alone will decide whether the patient is to be admitted into the hospital.

The history looks for clues to life-threatening causes of chest pain: myocardial infarction, unstable angina, pulmonary embolism, pneumothorax, mediastinitis , and aortic dissection.

It is important to obtain an accurate description of the pain's onset, duration, severity, nature, location, aggravating or alleviating factors, and prior episodes. Specifically it is important to note the presence or absence of radiation of pain and any associated symptoms (nausea, shortness of breath, sweats) and their severity.

The pain of angina or myocardial infarction builds up,

while aortic dissection and pulmonary embolism tend to cause "instant severe pain. Angina at rest has a very different prognosis from angina while running up the stairs. Pain starting as the patient swallows a bolus of food suggests esophageal pain.

The duration of the pain also helps establish the cause. Pain that lasts only a second or two, or pain that is constant for many days, is almost never cardiac pain. Angina typically lasts five to 15 minutes - pain for less than a minute is unlikely to be angina.

The nature of the pain can suggest the diagnosis. A description of chest pain as poking, pinching, or stabbing usually means chest wall pain. Hyperventilation often causes poking pains that are migratory and unrelated to motion. Victims of aortic dissection will often describe a well-localized "tearing" type pain. However, when the patient has pain from the internal organs (heart, esophagus, gallbladder), the nature of the pain is unhelpful at best, and is often misleading: a victim of myocardial infarction may complain of "heartburn," while the patient with esophagitis may complain of a squeezing sensation.

Another important part is the location of the pain. Pain from the internal organs of the chest tends to be felt over a wide area. If the pain is small in area, located over the chest wall, and corresponds to an area of tenderness, it's probably chest wall pain. If the patient has several small and migratory locations of pain "like tiny pins" usually will reveal no organic disease.

History of radiation of the pain is also very crucial. Chest pain from reflux esophagitis, ulcer, or gallbladder will usually have an epigastric component, but rarely radiates to the arms. Aortic dissection usually hurts in the back. And of course, pain radiating to the jaw, shoulders, or arms suggests (but is not diagnostic of) cardiac pain.

Some external factors may affect the pain. Even breathing may make the pain worse. Three-fourths of pulmonary embolism victims will have pleuritic pain. Worsening with position or with motion of the arms is expected with chest wall pain, but can occur with any cause of pleuritic pain, such as pericarditis or pleurisy. If resting stops the pain, it is important to know how long it takes to go away. Angina will usually take a minute to ease, while other activity-related pains often stop instantly with rest.

A history of multiple episodes of the same pain, lasting hours each time, virtually excludes myocardial infarction. Any constant factors for these past episodes are important, such as: relation to meals or time of day, duration of pain, and factors affecting the pain.

When the history seems confusing, there may be more than one cause of chest pain. A patient with angina on exertion also may have musculoskeletal chest pain with activity, and may have "lumped" these pains into one. A patient with a MI after a meal may have had past episodes of heartburn or gallbladder pain after meals. Careful questioning about the exact sensations of specific episodes can help to avoid a mistaken diagnosis.

The entire history "snapshot" is required for a diagnosis. Histories specifically about recent melena, active ulcer disease, diabetes, recent major surgery, stroke, or brain tumors or vascular malformations are also very important.

Signs and Symptoms

- Typical heart attack pain occurs in the mid to left side of the chest and may also extend to the left shoulder, the left arm, the jaw, the stomach, or the back. Other associated symptoms are shortness of breath, increased sweating, nausea, and vomiting.
- Angina is classified as chest pain that is similar to that of a heart attack but occurs with increased exercise and is relieved by nitroglycerin taken under the tongue. Angina becomes life-threatening when pain occurs at rest, has increased in frequency or intensity, or is not relieved with at least 3 nitroglycerin tablets each given 5 minutes apart. This is considered to be unstable angina, which may be a warning sign of an impending heart attack.
- The chest pain associated with aortic dissection occurs suddenly and is described as "ripping." The pain may radiate to the back or between the shoulder blades. Because the aorta supplies blood to the entire body, people may experience symptoms such as chest pain, shortness of breath, fainting, abdominal pain, or symptoms of stroke.
- Symptoms of a pulmonary embolus are sudden onset of shortness of breath, rapid breathing, and sharp mid-chest pain, which increases with deep breaths.
- Signs and symptoms of pneumothorax are sudden onset of shortness of breath, sharp chest pain, rapid heart rate, and low blood pressure.
- Perforated viscus comes on suddenly with severe abdominal, chest, or back pain or pain in both places. ▶

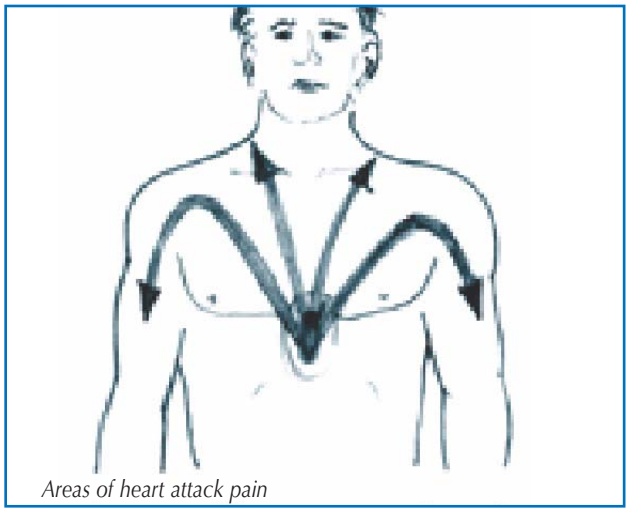
Abdominal pain may increase with movement or when breathing in and may be accompanied by a rigid, boardlike abdominal wall.

- The pain of pericarditis is typically described as a sharp or stabbing pain in the mid-chest area, worsened by deep breaths. This pain may mimic the pain of a heart attack, because it may radiate to the left side of the back or shoulder. One distinguishing factor is that the pain is worsened by lying flat and improved by leaning forward. When lying flat, the inflamed pericardium is in direct contact with the heart and causes pain. However, when leaning forward, there is a space between the pericardium and the heart. Prior to the onset of the chest pain, people may note having a recent cold, fever, shortness of breath, or pain when swallowing.
- Although mitral valve prolapse (MVP) is not usually associated with symptoms, people may experience palpitations and chest pain. Chest pain associated with MVP differs from that of typical angina in that it is sharp, does not radiate, and is not related to physical exertion. Other associated symptoms include fatigue, lightheadedness, and shortness of breath. Anxiety also seems to be more common in people with MVP than in the general population. Complications of MVP include infection of the heart valves, migraine headaches, stroke or mini-stroke, and abnormal heart rhythms, which rarely cause sudden death.
- Pneumonia may cause chest pain from the strain of the chest wall muscles during prolonged or forceful coughing.
- With chest pain originating from the esophagus, symptoms depend on the source.
- Symptoms of gastroesophageal reflux disease (GERD) include heartburn, painful swallowing, excessive salivation, dull chest discomfort, chest pressure, or severe squeezing pain across the mid chest. People may appear comfortable or may experience profuse sweating, pallor, nausea, and vomiting. Pain from GERD is often relieved with antacids.
- Symptoms of esophagitis include difficulty swallowing, painful swallowing, or symptoms of GERD. The associated chest pain comes on suddenly and is not relieved by antacids.
- The pain of esophageal spasm is usually intermittent and dull. It is located in the mid chest and may radiate to the back, neck, or shoulders.

The Physical Exam in Chest Pain

The most important part of the physical exam of the chest pain patient is the first "lookover." Poor skin color, diaphoresis, tachypnea, and anxious expression indicate to a potentially lethal process.

Tachycardia is non-specific - it can suggest shock, severe pain, or physical stress. Tachycardia is particularly likely with pulmonary embolism (PE). Blood pressure should be checked in both arms. A difference of over 20 mm Hg systolic suggests aortic dissection - and will be present in about two thirds of cases. Hypotension may suggest massive PE or cardiac shock. Fever may suggest pneumonia or mediastinitis as the cause of chest pain. Tachypnea may simply reflect severity, or can suggest pulmonary embolism or hyperventilation.



Areas of heart attack pain

Examination should seek general evidence of atherosclerosis [or risk factors for Atherosclerotic Vascular Disease (ASVD)]. It is important to note corneal lipid rings, narrowed retinal arteries, and pigment and hair changes in the legs.

The neck veins should be evaluated for distention. The carotids should be checked for quality of pulse, and for bruits. The chest wall should be inspected for respiratory motion, respiratory retractions or accessory muscle use, and precordial motion. It is important to identify the apical impulse. Tender areas to be felt. Many older patients will have tenderness. It is important for the diagnosis of musculoskeletal chest pain.

Lungs for rales, wheezes, and asymmetrical breath sounds should be noted. Asymmetry of breath sounds may be found in about half of patients with spontaneous pneumothorax. However, asymmetry also can be due to splinting of the painful side of the chest in other conditions that cause pleuritic pain. Wheezing will most likely be due to underlying COPD, but can occur due to heart failure (cardiac asthma) or pulmonary embolism.

It is also important to listen to the heart tones. Wide physiologic splitting of the second heart sound (splitting wider with inspiration) can be found in right bundle branch block or in right ventricular infarction. New paradoxical splitting is most often due to left bundle branch block, or anterior or lateral infarction. A new fourth heart sound (preceding the first heart tone) can occur with angina or infarction. An S3 (third heart tone) is more likely due to underlying heart failure.

A new murmur may be significant. Aortic regurgitation occurs in over half of patients with aortic dissection. New mitral regurgitation can occur in patients with angina or infarction, and is due to papillary muscle dysfunction.

The extremities should be examined for pulses, edema, calf tenderness, and signs of atherosclerotic vessel disease. Absence of pedal pulses may occur in aortic dissection. Any swelling of the legs, especially if unilateral, raises the odds of pulmonary embolism as the cause of chest pain. Pulmonary embolism often occurs in patients with CHF.

Diagnostic Maneuvers

Trial therapy of chest pain can be misleading. The placebo response may result in improvement of chest pain in about one fourth of chest pain patients, no matter what the intervention. The spontaneous improvement of pain may be attributed to a specific therapeutic trial, resulting in false diagnosis.

Patients with cardiac-compatible pain should be given sublingual nitroglycerin. About three fourths of patients with angina will have complete pain relief within two minutes. However, most patients with esophageal spasm also will have pain relief with nitroglycerin. Relief with nitroglycerin is not diagnostic of cardiac pain.

A "GI Cocktail" of antacid and lidocaine can be given for potential pain relief, but should not be relied on for diagnostic purposes. Only 25 percent of emergency patients with reflux esophagitis will have relief of pain with the GI cocktail. More ominously, about 20 percent of MI patients will report some relief of pain with the GI cocktail. The spontaneous resolution of an episode of unstable angina after administering a cocktail may lull the physician into making a mistaken diagnosis - one with potentially fatal consequences for the patient.

Diagnostic tests that may be performed include

- Electrocardiogram (ECG).
- Exercise ECG or Stress tests.
- Blood tests (such as LDH, LDH isoenzymes, CPK,CPK isoenzymes, Troponin, CBC, and blood differential)
- Chest X-ray.
- Nuclear scans.
- Coronary catheterization
- Electron beam computerized tomography (EBCT). Also called an ultrafast CT scan, scans the arteries for signs of calcium, which indicates that fatty deposits along with calcium may be accumulating and blocking arteries supplying the heart.
- Magnetic resonance imaging (MRI). Recent research has suggested that MRI may be an effective way to determine if a cardiac problem is causing chest pain.
- Echocardiogram.
- Endoscopy

Treatment of chest pain

Treatments for cardiac and non-cardiac causes of chest pain depend on the type of problem and must be treated accordingly.

Prevention methods for chest pain

Depending upon the nature of the underlying damage or abnormality causing some types of chest pain, prevention may be possible. For example, people may notice that they only experience chest pain in certain situations (e.g., when feeling "stress" or during "exercise"). They are encouraged to look for any patterns in their chest pain to find strategies for avoiding the problem as much as possible.

References

- Medline Plus
- Heartcenteronline.com
- Medical-library.org
- Heartprotect.com
- eMedicine

Meconium Aspiration Syndrome

Meconium Aspiration Syndrome (MAS) is a common problem faced by pediatricians and obstetricians. Meconium aspiration is defined as the presence of meconium below the vocal cords. This finding occurs in 20% to 30% of all infants with meconium-stained amniotic fluid. MAS classically has been defined as respiratory distress that develops shortly after birth, with radiographic evidence of aspiration pneumonitis and a history of meconium-stained fluid. More recently, MAS had been defined simply as respiratory distress in an infant born through meconium-stained amniotic fluid whose symptoms cannot otherwise be explained.

Infants born through meconium-stained amniotic fluid are about 100 times more likely to develop respiratory distress than those born through clear fluid. Even in women at very low risk for obstetric complications, meconium-stained amniotic fluid is common and is associated with a fivefold increase in perinatal mortality compared with low-risk patients with clear amniotic fluid. Death occurs in about 12% of infants with MAS, and MAS is associated with about 5% of all of perinatal deaths. MAS is also associated with neonatal seizures and chronic seizure disorders.

Epidemiology

Incidence:

In the USA: there are an estimated 520,000 births (12% of live births) complicated by meconium stained amniotic fluid. Of these, 35% will develop MAS (approximately 4% of all live births). 30% of babies with MAS will require mechanical ventilation, 10% develop pneumothoraces, and 4% die. More than 66% of all cases of persistent pulmonary hypertension (PPHN) are related to MAS.

In the developing countries: with less availability of prenatal care and where home deliveries are common, incidence of MAS is thought to be higher and associated with a greater mortality rate.

Race: no racial predilection exists.

Sex: MAS affects both sexes equally.

Age: MAS is exclusively a disease of newborns.

Risk Factors for MAS

Determining which infants are at high risk for MAS can allow more aggressive use of preventive measures or more timely institution of effective therapies. Five characteristics are to be significant risk factors for MAS:

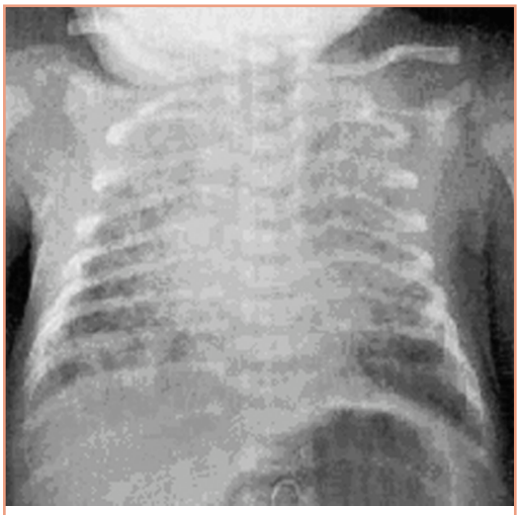
(1) Admission for induction with non-reassuring fetal heart rate pattern

(2) Need for endotracheal intubation and suctioning

(3) 1-minute Apgar score of 4 or less

(4) Cesarean delivery, and

(5) Previous cesarean delivery.



X-ray Chest showing diffuse chemical pneumonitis from constituents of meconium

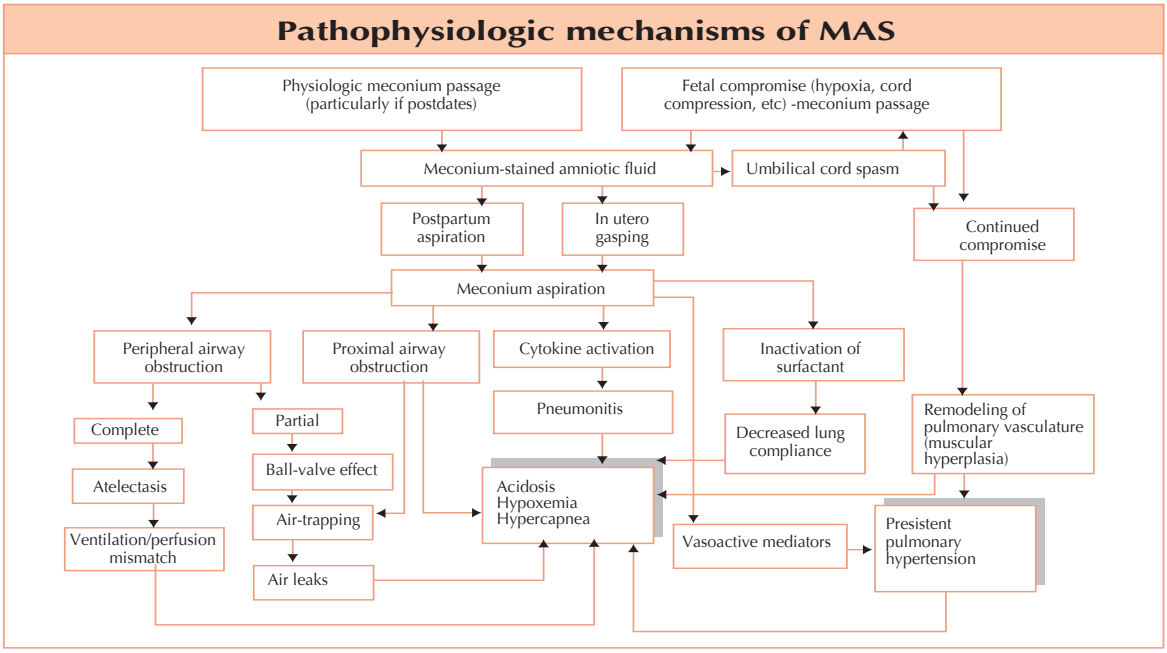
Causes

Etiology is not well understood. There are multiple causative factors of meconium passage which include the following:

- Placental insufficiency
- Maternal hypertension
- Preeclampsia
- Oligohydromnios
- Maternal drug abuse, especially of tobacco and cocaine.

Pathophysiology

The pathophysiology of meconium aspiration and MAS is complex, and the timing of the initial insult resulting in MAS remains controversial. Intrauterine fetal gasping, mechanical airway obstruction, chemical pneumonitis, surfactant inactivation, and damage of umbilical vessels all play roles in the pathophysiology of meconium aspiration. There is also a strong association between ▶



MAS and persistent pulmonary hypertension of the newborn (PPHN).

Clinical features of MAS

- Severe respiratory distress may be present. Symptoms include the following:
  - Cyanosis
  - End-expiratory grunting
  - Alar flaring
  - Intercostal retractions
  - Tachypnea
  - Barrel chest in the presence of air trapping
- Green urine may be observed in newborns with MAS less than 24 hours after birth. Meconium pigment can be absorbed by lung and excreted in urine.
- Signs: presence of meconium in amniotic fluid is essential to the initiation of the pathogenesis.

Differential diagnosis

- Pneumonia
- Sepsis with pulmonary edema
- Respiratory distress syndrome in a term infant
- Aspiration of amniotic fluid or blood
- Transient tachypnea of newborn
- Persistent pulmonary hypertension
- Acute respiratory distress syndrome
- Congenital cyanotic heart disease
- Pulmonary hypoplasia
- Transposition of the great arteries

Investigations

Lab studies

- Assessment of acid-base status:
  - Ventilation-perfusion (V-Q) mismatch and perinatal stress are prevalent
  - Metabolic acidosis from perinatal stress is complicated by respiratory acidosis from parenchymal disease and PPHN
  - Arterial blood gases measure pH, partial pressure of CO2 (pCO2), partial pressure of O2 (pO2), and continuous measurement of oxygenation by pulse oximetry are necessary for appropriate management.
- Serum electrolytes: sodium, potassium, and calcium concentrations should be measured when the infant with MAS is aged 24 hours because the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and acute renal failure are common complication of perinatal stress
- Complete blood count.

Imaging studies

- Chest radiograph is essential to
  - Determine the extent of intrathoracic pathology
  - Identify areas of atelectasis and air block syndromes
  - Assurance of appropriate positioning of an endotracheal tube and umbilical arterial catheter ▶

- When the infant is stable, imaging procedures of the brain, i. e. MRI, CT scan, or cranial ultrasound, are indicated if the infant's neurological findings are abnormal
- An echocardiogram ensures normal cardiac structure and assesses the severity of pulmonary hypertension and right-to-left shunting.

Management of MAS

Prevention

- Prevention is paramount
- Assessment of risk factors for MAS
- Continuous fetal monitoring to prevent and assuage fetal stress
- The early determination of meconium passage by amniotomy
- Upon delivery of the head of the baby, careful suctioning of the posterior pharynx decreases the potential for aspiration of meconium. When aspiration occurs, intubation and immediate suctioning of the airway can remove much of the aspirated meconium.

❑ *The following should not be done:*
- Squeezing the chest of the baby
- Inserting a finger in to the mouth of the baby
- Externally occluding the airway of the baby

❑ The American Academy of Pediatrics Neonatal Resuscitation Program Steering Committee has promulgated the following guidelines for management of the baby exposed to meconium:
- If the baby is not vigorous (Apgar 1-3): suctioning of the trachea must be done immediately after delivery (i.e. before many respirations have occurred). Suctioning should not be longer than 5 seconds. If no meconium is retrieved, repeated intubation and suction is not needed. If meconium is retrieved and no bradycardia is present reintubation and suction should be done. If heart rate is low, positive pressure ventilation and repeated suctioning should be tried.
- If the baby is vigorous (Apgar >5): secretions and meconium from the mouth and nose should be cleared with a bulb syringe or a large -bore suction catheter. In either case, the remainder of the initial resuscitation steps should ensue: dryness, stimulation, and administration of oxygen as necessary.

Intervention

- Optimum thermal environment must be kept
- Minimal handling of the infants because these infants are agitated easily and quickly become hypoxemic and acidotic
- Respiratory care must be taken. Oxygen therapy via hood or positive pressure is crucial in maintaining adequate arterial oxygenation. If mechanical ventilation is required, the mean airway pressure should be minimized to short an inspiratory time as possible. Use of surfactant has not yet been proven to be efficacious
- Oscillatory, high-frequency, and jet ventilation are effective alternative to conventional ventilation. Hyperventilation to induce hypocapnia and respiratory alkalosis is used as primary therapy for pulmonary hypertension. Nitric oxide inhalation has replaced the use to most intravenous pulmonary vasodilators
- Systemic blood volume and blood pressure (BP) should be monitored. Volume expansion, transfusion therapy, and systemic vasopressors are critical in maintaining systemic BP greater than pulmonary BP, thereby decreasing the right to left shunt through patent ductus arteriosus
- Extracorporeal membrane oxygenation (ECMO) is employed if all other therapeutic options have been exhausted
- Surgical care: a pediatric surgical consultation may be required in severe cases
- Diet:
  - Perinatal distress and severe respiratory distress preclude feeding
  - Intravenous fluid therapy begins with adequate dextrose infusion to prevent hypoglycemia
  - Progressive addition of electrolytes, protein, lipids, and vitamins to ensure adequate nutrition and prevention of essential amino acid and essential fatty acid deficiencies.

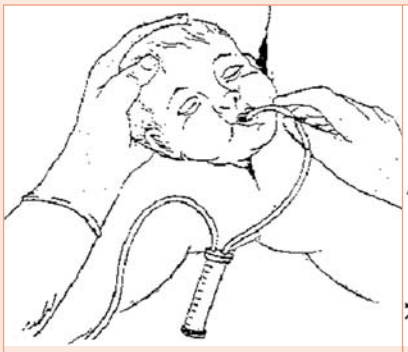
Complications

❑ A few infants with MAS have increased incidence of infections in the first year of life because the lungs are still recovering

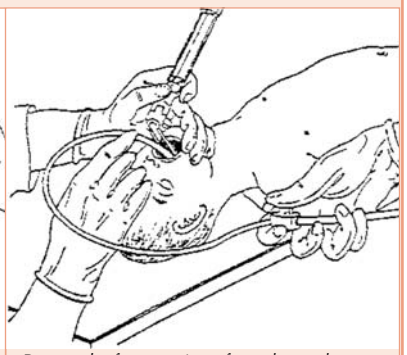
❑ Children with MAS may develop chronic lung disease as a result of intense pulmonary intervention.

Recommendations for the Prevention of Meconium Aspiration Syndrome

- ❑ All attendants at delivery should have expertise in evaluating and treating pregnancies complicated by meconium-stained amniotic fluid
- ❑ After detection of meconium, continuous fetal monitoring should be performed
- ❑ The delivery room should be prepared for pharyngeal suctioning, tracheal suctioning, and resuscitation. All equipment should be checked for proper working order
- ❑ After delivery of the head and before delivery of the shoulders, the mouth, nose, and pharynx should be suctioned with a large-bore (10F-14F) suction catheter using wall suction or a De Lee trap. A bulb syringe may be used if a catheter is not available
- ❑ If there has been evidence of fetal distress or thick meconium, or if infant vigor is depressed (poor muscular tone or heart rate below 100 beats per minute), the infant should be transferred immediately after delivery to a prepared warm environment. Assessment of infant vigor should be done immediately with no delay for assignment of Apgar score
- ❑ The vocal cords should be visualized with a laryngoscope, and any residual meconium in the hypopharynx or about the cords should be removed with a large-bore catheter.
- ❑ The trachea should then be intubated with the appropriate-sized endotracheal tube and the lower airway suctioned. Preferably, suction should be applied directly to the tube with a meconium aspirator as the tube is slowly withdrawn. A meconium aspirator with a continuous pressure of -80 to -150 mm Hg is most effective in removing meconium. A suction catheter should not be introduced through the endotracheal tube
- ❑ If a substantial amount of meconium is returned by suction, the intubation and suction should be repeated until there is clearing of aspirated material



Pharyngeal suctioning of an infant before delivery of the shoulders



Removal of meconium from hypopharynx and larynx using a large-bore catheter

- ❑ Alternatively, tracheal suctioning may be performed directly with a large-bore catheter, though this technique is more difficult than intubation
- ❑ Ventilation and other resuscitative measures should be used between episodes of suctioning if oxygenation is needed, even if the meconium has not been completely cleared
- ❑ After initial stabilization, the suction catheter may be advanced through the mouth to the stomach and the infant's stomach emptied of meconium that could later be regurgitated and aspirated.

Prognosis

- ❑ Nearly all infants with MAS have complete recovery of pulmonary function
- ❑ Events initiating the meconium passage may cause the infant to have long-term neurologic deficits, including CNS damage, seizures, mental retardation, and cerebral palsy.

References

- Maymon E, Chaim W, Furman B, Ghezzi F, ShohamVardi I, Mazor M. Meconium stained amniotic fluid in very low risk pregnancies at term gestation. Eur J Obstet Gynecol Reprod Biol 1998;80:169-73.
- Mathews TG, Warshaw JB. Relevance of the gestational age distribution of meconium passage in utero. Pediatrics 1979;64:30-1.
- Cialone PR, Sherer DM, Ryan RM, et al: Amnioinfusion during labor complicated by particulate meconium-stained amniotic fluid decreases neonatal morbidity. Am J Obstet Gynecol 1994 Mar; 170(3): 842-9.
- Clark DA, Nieman GF, Thompson JE, et al: Surfactant displacement by meconium free fatty acids: an alternative explanation for atelectasis in meconium aspiration syndrome. J Pediatr 1987 May; 110(5): 765-70.
- Kinsella JP: Meconium aspiration syndrome: is surfactant lavage the answer?. Am J Respir Crit Care Med 2003 Aug 15; 168(4): 413-4.
- Nathan L, Levino KJ, Carmody TJ 3rd, Kelly MA, Sherman ML. Meconium: a 1990s perspective on an old obstetric hazard. Obstet Gynecol 1994;83:329-32.
- Wiswell TE, Henley MA. Intratracheal suctioning, systemic infection, and the meconium aspiration syndrome. Pediatrics 1992;89:203-6.
- Meconium Aspiration syndrom; May 26, 2004. emedicime.com
- Mary Celeste Klingner, Jerry Kruse. Meconium Aspiration Syndrome. pathophysiology and prevention. J Am Board Fam Pract 12(6): 450-466, 1999.
- Katz VL, Bowes WA Jr. Meconium aspiration syndrome: reflections on a murky subject. Am J Obstet Gynecol 1992;166(1 Pt 1):171-83.
- Miller FC, Read JA. Intrapartum assessment of the postdate fetus. Am J Obstet Gynecol 1981;141:516-20.
- Lucas A, Adrian TE, Aynsley-Green A, Bloom SR. Gut hormones in fetal distress. Lancet 1979;2:968.
- Lucas A, Christofides ND, Adrian TE, Bloom SR, Aynsley-Green A. Fetal distress, meconium, and motilin. Lancet 1979;1:718.

A fever isn't an illness itself, it's usually a sign of infection, inflammation, malignancy or other diseases. It is part of our body's defense mechanism. For an adult, a fever may be uncomfortable, but it usually isn't dangerous unless it rises above 39.4° C. For very young children and infants, however, even slightly elevated temperatures may indicate a serious infection. In newborns, a subnormal temperature, rather than a fever, may be a sign of serious illness. By producing a low-grade fever body may actually be helping eliminate the virus. Most fevers go away in a relatively short time - usually within a few days.

Pathophysiology

Abnormal elevations of temperature are due to either hyperthermia or fever. Hyperthermia results from failure of thermal control mechanisms. Hyperthermia is not mediated by cytokines. It occurs when body metabolic heat production or environmental heat load exceeds normal heat loss capacity or when there is impaired heat loss; heat stroke is an example. Body temperature may rise to levels (>41°C) capable of producing irreversible protein denaturation and resultant brain damage; no diurenal variation is observed.

In fever, thermoregulatory mechanisms are intact, but the hypothalamic set point is elevated above normal by exogenous or endogenous pyrogens. When proper stimuli act on appropriate monocyte-macrophages, these cells elaborate pyrogenic cytokines, causing elevation of the set point through effects in the hypothalamus. These cytokines include interleukin-1 (IL-1), tumor necrosis factor (TNF), interferon-gamma and interleukin-6 (IL-6). The elevation of temperature results from either increased heat production or decrease loss.

Response to fever varies with age. In the elderly, inadequate thermoregulatory mechanisms may contribute to hyperthermia and result in arrhythmias, ischemia, mental status changes, or heart failure from increased metabolic demands. In children between the ages of 6 months and 6 years, febrile convulsions may occur.

Causes of fever

Common causes

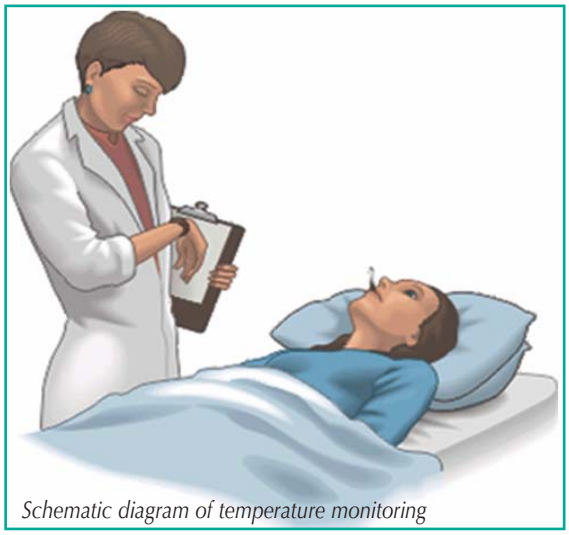
- Infections: bacterial, viral, rickettsial, fungal, parasitic
- Autoimmune diseases
- Central nervous system disease,including head trauma and mass lesions
- Malignant disease, especially renal cell carcinoma, primary or metastatic liver cancer, leukemia, and lymphoma.

Less common causes

- Cardiovascular diseases, including myocardial infarction, thrombophlebitis, and pulmonary embolism
- Gastrointestinal diseases, including inflammatory bowel disease, alcoholic hepatitis, and granulomatous hepatitis
- Miscellaneous diseases, including drug fever, sarcoidosis, familial Mediterranean fever, tissue injury, hematoma, and factitious fever.

Hyperthermia

Peripheral thermoregulatory disorders, including heat stroke, malignant hyperthermia of anesthesia, and malignant neuroleptic syndrome



Schematic diagram of temperature monitoring

Clinical Features

Symptoms:

- Feeling hot: objective evidence of raised body temperature should be taken
- Rigors: shivering implies a rapid rise in body temperature
- Excessive sweating: night sweats are characteristics of tuberculosis, but sweating from any cause usually worse at night. Alcohol misuse, anxiety, thyrotoxicosis, diabetes mellitus are the non-infective case of sweating
- Headache: fever from any cause may provoke headache. Severe headache, photophobia are characteristics of meningitis, but headache may be ▶

present in pyelonephritis, pneumonia and bacterial enteritis

- ❑ Delirium: mental confusion during fever is relatively more common in young children and the elderly
- ❑ Muscle pain: myalgia is characteristic of viral infections such as influenza and enterovirus infection, but may also accompany septicemic illness including meningococcal disease

Signs:

Rash: A purpuric or petechial rash suggests meningococcal disease but some patients with this infection have an erythematous (blanching) rash, or no rash at all; differential diagnosis includes petechiae induced by vomiting (superior vena cava distribution), Henoch-Schonlein purpura, vasculitic drug reactions and thrombocytopenia.

Vesicular rashes may be caused by chickenpox, coxsackie A virus infection (hand, foot and mouth disease) and erythema multiforme.

Parvovirus B19 infection produces an erythematous or lace-like rash and a characteristic 'slapped cheek' appearance.

Oral temperature: Raised oral temperature. The equilibrium time with a mercury in glass thermometer is a minimum of 90 seconds.

Mouth and oropharynx: Palatal petechiae or cheesy grey-white tonsillar exudate suggests infectious mononucleosis.

Neck stiffness: Stiffness in forward flexion implies meningeal irritation; stiffness in all directions suggests local disease of the spine or soft tissues.

Cervical lymph nodes: Enlargement of anterior and tonsillar nodes is usually associated with tonsillitis or pharyngitis, posterior lymphadenopathy may suggest a glandular fever syndrome or HIV infection.

Renal angle tenderness: True renal tenderness is difficult to distinguish from lumbar myalgia which occurs in many systemic viral and bacterial infections.

Assessment

Assessment of fever requires careful history taking, medication review, and physical examination that includes all major body systems. Individuals with suspected infection, especially those with neutropenic fever, should undergo meticulous evaluation of the skin, all body orifices (i.e., mouth, ears, nose, throat, urethra, vagina, rectum), finger stick and venipuncture sites, biopsy sites, and skin folds (i.e., breasts, axilla, groin). Oral assessment includes evaluation of the teeth, gingiva, tongue, floor of the mouth, nasopharynx, and sinuses. The perirectal area is a common source of infection, especially in individuals with leukemia. Vascular access devices (VAD) and other artificial indwelling devices (i.e., percutaneous nephrostomy tubes, biliary drainage tubes, gastrostomy or jejunostomy tubes) are other commonly implicated sources of infection. Urine, sputum and blood cultures (peripheral and from ports or lumens of VADs), and radiographic imaging with chest radiography, and as directed by the above findings, complete the initial evaluation. Individuals undergoing cytotoxic chemotherapy should be instructed to seek immediate medical attention if they develop fever when neutrophil counts are low or declining. Frequent reassessment, including physical examination, is especially important in the neutropenic host, as signs and symptoms of infection may be minimal. Evaluation for recurrent or progressive tumor can be performed at the same time as evaluation for potential infection and other causes of fever.

Guidelines for evaluating children with fever:

- ❑ Child should be assessed immediately if:
  - The child is under 2 months old
  - The fever is >40.1°C
  - The child is crying inconsolably or whimpering
  - The child cries when moved or otherwise touched by the parent
  - The child is difficult to awaken
  - The neck is stiff
  - Any purple spots are present on the skin
  - Breathing is difficult, and no better after the nose is cleared
  - The child is drooling saliva and is unable to swallow anything
  - A convulsion has occurred
  - The child acts or looks very sick.
- ❑ Child should be assessed within 24 hours if:
  - The child is 2 to 4 months old (unless fever occurs within 48 hours of a DPT vaccine and the infant has no other serious symptoms)
  - The fever exceeds 40° C (especially if the child is <3 years)

- Burning or pain occurs with urination
- The fever has been present >24 hours without an obvious cause or location of infection
- The fever went away for >24 hours and then returned
- The fever has been present for >72 hours.

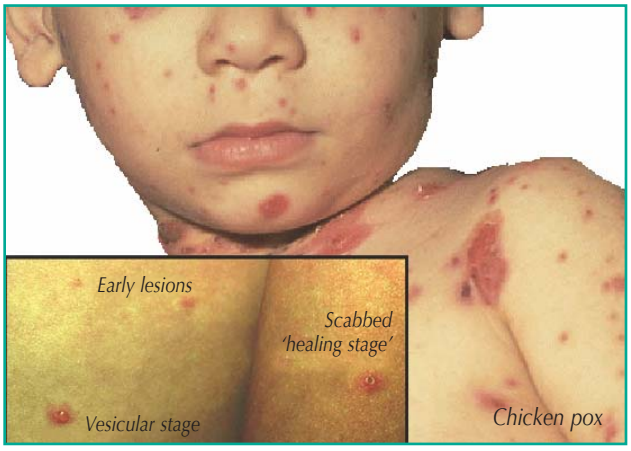
Evaluation of the febrile child and outpatient bacteremia: children who are at increased risk for serious bacterial illness (SBI) must be identified and treated accordingly.

Essentials of diagnosis:

❑ Child less than 3 years of age with fever

❑ No focal infection found on physical examination.

Children under the age of 3 years who present with fever but no obvious source of infection present a special challenge to the physicians. Both minor illness and serious bacterial illness (SBI) i.e. sepsis, meningitis,



urinary tract infections, pneumonia, septic arthritis/osteomyelitis, enteritis are common at this age. In general, the height of the fever increases, the risk of SBI increases. In infants younger than 30 days, the rate of SBI was found to be 4.4% for temperatures 38.1 - 39°C, 7.6% for 39.1 - 39.9°C, and 18% for temperatures of 40°C or more. Various studies found the risk of occult bacteremia in children 3-36 months of age with fever without source to be from 3% to 11%.

❑ *Common bacterial pathogens cause invasive illness in children are*:

- Less than 2 months of age: group B *Streptococcus*, *Escherichia coli*.
- Older children: *Streptococcus pneumoniae*, *Haemophilus influenzae* type b

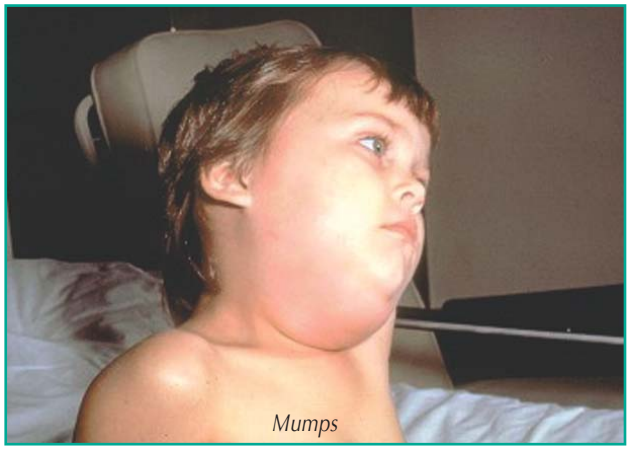
❑ Other organisms: *Staphylococcus aureus*, *Salmonella* spp. and other gram-negative organisms.

Treatment:

Most of the cases fever is well tolerated. When temperature is greater than 40° C symptomatic treatment should be given. Temperature over 41° C is likely to be hyperthermia (heat stroke) and not cytokine mediated, and emergency management is indicated.

Fever phobia and the over treatment of fever: many anxious parents treat low grade fever unnecessarily. The parents or attendants should be taught when to treat fever.

Antipyretic medications: antipyretic therapy is indicated in patients with marginal hemodynamic status. Aspirin or paracetamol/acetaminophan, 325-650 mg every 4 hours, is effective in reducing fever, These drugs are best administered continuously than as needed. Paracetamol is



indicated for children older than 2 months of age if the fever is >39°C and/or the child is uncomfortable. It can be given every 4-6 hours and will reduce the fever by 1-2° C within 2 hours of dose.

Liquid ibuprofen and paracetamol are similar in their ability to reduce fever. Ibuprofen lasts 6-8 hours. Aspirin should be used with caution in children and it is best to avoid in chickenpos or influenza due its link to Reye's syndrome.

Antimicrobial agents: in most febrile patients, empirical antibiotic therapy should be indicated for febrile patients who are clinically unstable, even before infection can be documented. These include patients with hemodynamic instability, those with neutropenia (PMN <500/µL), who are asplenic, immunosuppressed, and those who are HIV ▶

infected. For treatment of fever during neutropenia following chemotherapy, outpatient parenteral antimicrobial therapy with an agent such as ceftriaxone can be provided effectively and safely. If a fungal infection is suspected in a patient with prolonged fever and neutropenia, fluconazole is equally effective but less toxic toxic to Amphotericin B. Following principles should be considered before starting empirical antibiotic therapy:

- ❑ Antibiotics should not be given for virus infections such as colds and minor sore throats
- ❑ Antibiotics must be avoided if there is a risk of masking serious sepsis such as endocarditis, e.g. in a febrile patients with a heart murmur
- ❑ If possible, diagnostic specimens, e.g. a mid-stream sample of urine should be taken, before starting treatment
- ❑ Penicillin especially amoxicillin or ampicillin should be avoided in young patients with sore throats unless infectious mononucleosis has been excluded, because of the higher risk of drug rash. Erythromycin is the drug of choice in this situation
- ❑ The result of therapeutic trials may be false negative due to antibiotic resistance, inadequate tissue levels, poor compliance or undiagnosed deep sepsis. False positives are usually due to spontaneous resolution of fever.

Sponging for fever: indications for immediate sponging with lukewarm water (never alcohol) are febrile delirium, febrile seizure, or any fever over 41.1° C. Paracetamol should always be given 30 minutes prior to sponging. Until paracetamol has taken effect, sponging will only cause shivering, which may ultimately raise the temperature. Heat stroke requires immediate cold-water sponging, antipyretics are not beneficial.

Other measures: extra fluids should be encouraged. Body fluids are lost during fever because of sweating, and the increased respiratory rate associated with fever means increased insensible losses through respiratory vapors.

Management of "fever without source" in infants and children <3 years of age:

- ❑ Child who appears toxic should be hospitalized
- ❑ The neonates should be hospitalized. Infants under 1 month of age should have a sepsis workup and be hospitalized, even though the risk of SBI, if they meet the low-risk criteria below, is quite small. Generally the hospitalized infant is placed on parenteral antibiotics pending culture results; however, they could also be observed in the hospital without antibiotics
- ❑ Criteria of low-risk febrile infant (1-3 months of age):
  - Nontoxic
  - Previously healthy
  - No bacterial focus on examination (except otitis media)
  - Good social situation
  - WBC count 5000-15000/mm^3
  - Urinalysis with fewer than 5 WBCs/hpf
  - If diarrhea is present, fewer than 5 WBCs/hpf in stool.
- ❑ The low-risk infant (1-3 months of age) whose probability of an SBI is 0.2%, should be managed as an outpatient with one of the two options:
  - Urine culture should be reevaluated in 24 hours
  - Blood, urine, CSF should be cultured; ceftriaxone, 50 mg/kg should be administered and reevaluated in 24 hours.
- ❑ The non-low-risk febrile infant should be hospitalized
- ❑ The temperature of the previously healthy child 3 months to 3 years should be determined. If the fever is <39° C, antipyretics should be given and child should be followed up. If the temperature is 39° C or above, a WBC count should be done. If the count is at least 15000/mm^3, a blood culture should be done and ceftriaxone 50 mg/kg should be administered. Males under 6 months of age and females under 2 years of age should also have a urine specimen for culture. X-ray chest and stool culture are useful only if indicated by history or examination.

Prevention

The best way to prevent fevers is to reduce exposure to infectious diseases. Proper health education should be given to patient and parent or attendent.

Complication

Generally febrile seizure in case of children, but the complications depend on the cause of fever.

References

- Davidson's Principles and Practice of Medicine;19th edition
- Current Medical Diagnosis & Treatment; 43rd Edition; 2004
- Current Pediatric Diagnosis & Treatment; 13th edition
- American Academy of Family Physician; 2004
- Prof. M R Khan. Essence of Pediatrics; 2nd edition
- American Academy of Pediatrics; 2000
- BMJ; 1997; 314:1875 (28 June)

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Hyperthyroidism- Graves' Disease

Thyroid is the most important endocrine gland and the thyroid axis is involved in the regulation of metabolism. Various types of thyroid disease are common, affecting about 5% of the population, predominantly females. The major manifestations of thyroid disease are hyperthyroidism, hypothyroidism and goiter. The patient is likely to be a middle aged female but no age group is exempt. Iodine deficiency was found to be hyperendemic in Bangladesh in 1993 in the national survey on goiter.

Classification of thyroid disease

	Primary	Secondary
Hormone excess	◆ Graves' Disease ◆ Multinodular goiter ◆ Adenoma ◆ Subacute thyroiditis	Pituitary TSHoma
Hormone deficiency	◆ Hashimoto's thyroiditis ◆ Atrophic hypothyroidism	Hypopituitarism
Hormone resistance	◆ Thyroid hormone resistance syndrome ◆ 5`-monodeiodinase deficiency	
Non-functioning tumors	◆ Differentiated carcinoma ◆ Medullary carcinoma ◆ Lymphoma	

Immunologically thyroid diseases are classified into two groups:

- Autoimmune thyroid disease (AITD): classic AITDs are Graves' disease, Hashimoto's thyroiditis, atrophic, silent, and postpartum thyroiditis. Antimicrosomal antibody (anti-MIC) is highly specific for AITD. AITD is not uncommon in Bangladesh, the prevalence of AITD among thyroid patients was 48.36%.
- Non-autoimmune thyroid disease (NAITD)

HYPERTHYROIDISM- GRAVES' DISEASE

Graves' disease is an autoimmune disease named after Robert J. Graves, MD, approximately 1830s. The disease is characterized by hyperthyroidism due to circulating autoantibodies thyroid-stimulating immunoglobulins (TSIs). These TSIs bind to and activate the thyroid stimulating hormone (TSH) receptors, causing the thyroid gland to enlarge and increase synthesis of thyroid hormone from thyroid follicles. In some cases, Graves' disease represents a part of a more extensive autoimmune process, autoimmune polyglandular syndrome which is associated with pernicious anemia, vitiligo, diabetes mellitus type-I (IDDM), autoimmune adrenal insufficiency, and systemic lupus erythematosus.

Epidemiology

Incidence: Graves' disease is the most common causes of spontaneous thyrotoxicosis. The frequency of Graves' disease as the cause of thyrotoxicosis ranges from approximately 60-90% in different regions of the world. In the United States, the most common hyperthyroidism is Graves' disease, and an estimated incidence is approximately 30 cases per 100,000 persons per year, incidence of maternal thyrotoxicosis is approximately 1 case per 500 persons, and the most common cause of maternal Graves' disease. In the United Kingdom, the incidence is reported as 100-200 cases per 100,000 populations per year. The incidence in women is to be 80 cases per 100,000 women per year.

Race: susceptibility of Graves' disease is influenced by genes in the HLA region on chromosome 6 and CTLA-4 on chromosome 2q33. Association with specific HLA haplotypes has been observed and is found to vary with ethnicity.

Sex: like other autoimmune diseases, susceptibility is increased in females, female to male ratio is 7-8:1.

Age: typically it is a disease of young women, but it may occur at any age. The typical age range is 20-40 years.

Causes

It is autoimmune in etiology and influenced by a combination of environmental and genetic factors. CTLA-4 plays a very important role. Genetic factors contribute approximately 20-30% of overall disease susceptibility. Environmental factors associated with susceptibility are largely unproven. The possible factors are infection (*Yersinia enterocolitica*), iodide intake, stress, sex steroids, and toxins. Smoking has been implicated in the worsening of Graves' ophthalmopathy.

Pathophysiology

In Graves' diseasse (GD) B- and T-lymphocyte-mediated autoimmunity are known to be directed at thyroid antigens, thyroglobulin, thyroperoxidase, sodium-iodide symporter, and the TSH receptor. However, the TSH receptor itself is the primary autoantigen of Graves' disease and is responsible for the manifestation of hyperthyroidism. The stimulating activity of TSH receptor antibodies is found mostly in the immunoglobulin G1 (IgG1) subclass. These thyroid-stimulating antibodies cause release of thyroid hormone and thyroglobulin that is mediated by cyclic AMP, and they stimulate iodine uptake, protein synthesis, and growth in the thyroid gland. Graves' ophthalmopathy is still not well understood, and its precise relationship to Graves' hyperthyroidism has yet to be worked out. However the retroorbital fibroblast is now emerging as the most likely target cell, with ▶

retroorbital muscle involvement possibly secondary.

Clinical features

Patients usually present with the features of thyrotoxicosis:

- Goiter: diffuse, bruit or thrill may be present
- Ophthalmopathy: is present in 50% of patients, and is more common in cigarette smokers. Features are lid retraction, lid lag, grittiness, excessive lacrimation, ophthalmoplegia, diplopia, papilloedema, loss of visual acuity
- Gastrointestinal: weight loss despite normal or increased appetite, hyperdefecation, diarrhea & steatorrhea, anorexia, vomiting
- Cardiorespiratory: palpitation, sinus tachycardia, atrial fibrillation, increased pulse pressure, ankle edema in absence of cardiac failure, angina, cardiomyopathy & cardiac failure, dyspnea on exertion, exacerbation of asthma
- Neuromuscular: nervousness, irritability, emotional lability, psychosis, tremors, hyper-reflexia, ill-sustained clonus, muscle weakness, proximal myopathy, bulbar myopathy, periodic paralysis (predominantly Chinese)
- Dermatological: increased sweating, pruritus, palmar erythema, spider nevi, onycholysis (in the forth and fifth fingernails), alopecia, vitiligo, digital clubbing, pretibial myxedema
- Reproductive: amenorrhea, oligomenorrhea, infertility, spontaneous abortion, loss of libido, impotence
- Other: heat intolerance, fatigue, apathy, gynecomastia, lymphadenopathy, thirst, osteoporosis

Diagnosis

Diagnosis of Graves' disease may be straightforward, since the "classic face" with its triad of hyperthyroidism, goiter, and exophthalmos is easily recognized. Diagnosis of hyperthyroidism requires two steps: 1) confirmation of thyroid hormone excess and, 2) verification of Graves' disease as its cause.

Biochemical markers: biochemical diagnosis of thyrotoxicosis requires the combination of suppressed TSH levels and elevated thyroid hormone concentrations. Suppression of TSH is an early and highly sensitive marker of thyrotoxicosis. Mild excess of thyroxine (T4) or triiodothyronine (T3) usually leads to extreme suppression (to <0.1 micro IU/mL). Less marked suppression of TSH (0.1 to 0.4 micro IU/mL) more often reflects drug effects, sick euthyroid syndrome, or other such transient processes, or patients with less severe or slowly progressive thyroid disorders eg, toxic multinodular or uninodular goiter.

Total and free T4 values are usually in the normal to highnormal range when TSH suppression is borderline, and clinical signs and symptoms are absent or mild. In contrast, extreme suppression of TSH, coupled with markedly elevated T4 values and thyrotoxic symptoms, is common with overt Graves' disease.

A number of methods are used to measure thyroid hormones, and normal values vary among laboratories. Total T4 values in excess of 12 micrograms/dL provide supportive evidence for thyrotoxicosis. Values of 16 to 40 micrograms/dL usually indicate more severe thyroid dysfunction. Mildly elevated total T4 values (13 to 15 micrograms/dL) are not specific for thyrotoxicosis or Graves' disease and may simply represent situations in which thyroid-binding globulin (TBG) levels are high (eg, pregnancy, oral contraceptive use, other states of TBG excess). In such cases, TSH is not suppressed and thyrotoxic symptoms and signs are absent.

New assays for direct measurement of free T4 are rapid and reproducible and reflect true hormone excess without being influenced by TBG excess. Many clinicians are now using these quantitative determinations of free T4 instead of older methods that rely on estimates based on calculated products of resin T3 uptake (RT3U) and total T4. The latter approach may be inaccurate in certain circumstances, such as with sick euthyroid syndrome, drug effects, or acute psychiatric illness. Measurement of T3 by radioimmunoassay (RIA) can precisely confirm high concentrations of active hormone at the tissue level, where T4 is converted to T3.

Causes of thyrotoxicosis: patients with Graves' disease usually report several months of thyrotoxic symptoms, with steadily more severe and expansive multisystem involvement. The presence of a symmetric, smooth goiter is highly suggestive of Graves' disease, and ophthalmopathy or dermopathy confirms the diagnosis. In thyrotoxic patients without goiter or eye or skin signs, diagnosis of Graves' disease is suggested by elevated thyroid-stimulating immunoglobulin (TSIg) levels, antimicrosomal antibody (AMA) titers, or antithyroid peroxidase (anti-TPO) titers.

Other tests: CT scan or MRI of the orbits: may be necessary in the evaluation of proptosis.

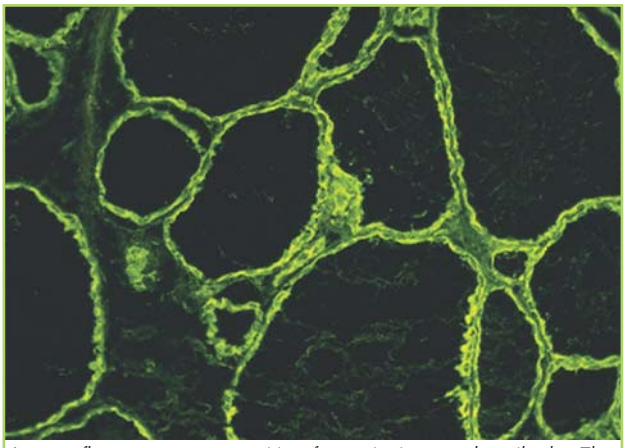
Histological findings: thyroid gland from patients with Graves' disease show lymphocytic infiltrates and follicular hypertrophy, with little colloid present.

Differential diagnosis

Anxiety neurosis, Menopause, Pheochromocytoma, Drug abuse or withdrawal, Myopathies, Thyrotoxicosis without hyperthyroidism.

Treatment

Medical therapy: antithyroid drugs available for treating Graves' disease are propylthiouracil (PTU), carbimazole and its active metabolite, methimazole. These drugs reduce thyroid hormone synthesis by interfering with iodination of tyrosine and PTU has the added benefit of blocking the peripheral conversion of T4 to T3. Beta blockers, such as propranolol hydrochloride in a starting dose of 10 to 20 mg four times daily, quickly control catecholamine-augmented thyrotoxic symptoms of Graves' disease. Beta blockers must be used along with antithyroid drugs for 2-4 weeks until preformed glandular hormone is metabolized, they are useful in symptomatic management during the 3-6 weeks of preparation for surgery or during the 2-6 months after radioiodine ablation.



Immunofluorescence test positive for anti-microsomal antibody. The bright green fluorescence in the thyroid epithelial cells, whereas the colloid in the center of the follicles is dark.

Radioactive iodine: use of radioactive iodine (RAI) is an effective method for treating hyperthyroidism. The dose of iodine 131 is based on estimated gland size. Goals of RAI treatment vary from hypothyroidism to restoring euthyroidism.

Surgery: surgical thyroidectomy was a popular treatment option in the past but is now used less often because of the success of RAI. Thyroidectomy is the treatment of choice in patients with very large goiters, since they may not respond adequately to RAI. Surgery is also appropriate for patients who wish to become pregnant or those with severe reactions to antithyroid drugs.

Special situations in hyperthyroidism

Thyroid crisis or thyroid storm: is a rapid deterioration of hyperthyroidism with hyperpyrexia, severe tachycardia and extreme restlessness. It is a rare condition, with a mortality rate of 10%. It is usually precipitated by stress, infection, surgery in an unprepared patient, or radioiodine therapy. Treatment is urgent with propranolol in full doses together with potassium iodide, antithyroid drugs, corticosteroids and full supportive measures.

The fetus and maternal Graves' disease: any mother with a history of Graves' disease may have circulating TSI. Even if she has been treated e.g. by surgery, the immunoglobulin may still be present. TSI crosses the placenta and stimulate the fetal thyroid, and the fetus can thus become hyperthyroid, while the mother remains euthyroid. The patient must be monitored during pregnancy. Fetal heart rate provides a direct biological assay of fetal thyroid status. Fetal heart rate over 160/min. are strongly suggestive of fetal hyperthyroidism. Maternal treatment with carbimazole and or propranolol may be used. To prevent the mother becoming hypothyroid, T4 may be given as T4 does not cross the placenta. If necessary surgery can be performed, preferably in the 2nd trimester. Radioactive iodine is absolutely contraindicated. Sympathomimetics are contraindicated as they may provoke fatal tachycardia in the fetus. The pediatrician should be informed and the infant should be checked immediately after birth. Overtreatment with carbimazole can cause fetal goiter. Breast feeding on usual dose of carbimazole or propylthiouracil appears to be safe.

Hyperthyroidism may also develop in the neonate as TSI has a half-life of approximately 3 weeks. Manifestations in the newborn include irritability, failure to thrive and persisting weight loss, diarrhea, and eye signs. Thyroid function tests are difficult to interpret as neonatal normal ranges vary with age. Untreated neonatal hyperthyroidism is probably associated with hyperactivity in later childhood.

Long-term consequences of hyperthyroidism

The only long-term risk of adequately treated hyperthyroidism appears to be an increased risk of osteoporosis.

References:

- Davidson's Principles and Practice of Medicine; 19th Edition
- Kumar & Clark Clinical Medicine; 5th Edition
- Michael W. Felz, MD; Peter P. Stein, MD. The many 'faces' of Graves' disease; Postgrad Med J 1999; Vol 106(5); 45-52
- M A Hasanat, M A K Rumi, M N Alam, K Nadim Hasan, M Salimullah, M A Salam, M Fariduddin, Hajera Mahtab, A K Azad Khan, Status of antithyroid antibodies in Bangladesh; Postgrad Med J 2000; 76:345-349
- Graves Disease, January 30, 2002; emedicine.com, on September 13, 2004
- Volpe MD R. The pathogenesis of Graves' disease; Endocr Pract. 1995; 1(2): 103-115

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Product Profile- Force®

Force® (Cefpirome) is a fourth generation cephalosporin antibiotic that has an extended spectrum of activity to include *Pseudomonas aeruginosa* and Gram-positive organisms including methicillin-sensitive *Staphylococcus aureus*, coagulase-negative *Staphylococci* and *Enterococcus* faecalis.

Composition: **Force®** (Cefpirome) 1 gm IV injection: Each vial contains sterile powder mixture of Cefpirome Sulphate INN (equivalent to 1 gm of Cefpirome) and anhydrous Sodium Carbonate BP.

Indication:

- Severe infections, such as septicemia, bacteremia and infections in immunosuppressed neutropenic patients with hematological malignancies
- Lower respiratory tract infections including pneumonia
- Severe urinary tract infections including pyelonephritis
- Skin and soft tissue infections
- Bone and joint infections
- Infections in immunocompromised patients
- Other infections

Dosage and Administration

Force® (Cefpirome) is administered only through the parenteral route. The dosage is dependent upon the severity and site of infection, the susceptibility of the infecting microorganisms and age, weight and renal function of the patient. The drug is administered through intravenous Injection or infusion. The following dosages are recommended for moderate to severe infections in adult patients with normal renal function:

Indication	Unit dose (g)	Dosage interval (hrs)	Total daily dose (g)
Complicated upper & lower urinary tract infections	1	12	2
Skin & soft tissue infections	1	12	2
Lower respiratory tract infections	1 to 2	12	2 to 4
Bacteremia/septicemia and severe infections	2	12	4
infections in neutropenic patients	2	12	4

Dose reduction is necessary in patients with markedly reduced renal function. After an initial dose of 0.5 -2g to establish a high serum concentration, the dose should be reduced by 50% for clearances of 49-21 ml/min or 75% for clearances of 20 ml/min. In end-stage renal disease, a supplementary dose equal to 50% of the recommended daily dose should be administered after each hemodialysis treatment.

Duration of treatment: The duration of treatment depends on the patient's clinical and bacteriological response.

Route of administration: Intravenous route only.

Contraindications: Cefpirome is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Adverse reactions: Cefpirome is generally well tolerated. There are no predictable life threatening effects of Cefpirome. Adverse gastrointestinal reactions include diarrhea, nausea, vomiting, pseudomembraneous colitis, and abdominal pain have been noted 3.86% of the patients. Superficial phlebitis, thrombophlebitis and infection site reaction have been reported in 2.31 % of patients receiving intravenous Cefpirome.

The elderly: There are no special precautions for its use in the elderly provided dosage is adjusted accordingly to renal function.

Pregnancy & Lactation: The safety of Cefpirome has not been established in pregnancy and as with all agents it should be administered with caution, especially during the early months of pregnancy.

As Cefpirome is excreted in human breast milk, either Cefpirome treatment should be discontinued or breast-feeding ceased.

Acute Over Dosage: No cases of over dosage are known. However, general supportive care with monitoring of renal, hematological and hepatic function and coagulation status is recommended.

Drug Interactions: Drug Interactions have not been observed with Cefpirome.

Storage Condition: Force® (Cefpirome) vial should be stored below 25^{0}C protected from light. Freshly reconstituted solution is always recommended. Reconstituted solution can be stored for up to 6 hours at room temperature (up to 25^{0}C and in indoor light) and 24 hours in refrigerator (at 2-8^{0}C) when prepared in water for injection BP.

How Supplied: Force® 1 gm IV injection: Inner pack: Each pack contains 1 vial of Cefpirome 1gm as Cefpirome sulphate INN accompanied by a solvent ampoule of 10 ml water for Injection BP. Outer pack: Each pack contains 1 inner pack and a 10 ml disposable syringe.

Correct answers of the 'Test Yourself - 16'

1. b,d **2.** a **3.** a,d **4.** a **5.** c,d **6.** b,c

The following are the 10 winners of the "Test Yourself -16"; they have been selected through lottery.

Congratulations from "the SQUARE" Editorial Board

Dr. Md. Allama Iqbal
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General Hospital, Jamalpur

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MBBS
UHFPO, Lohagara
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Dr. Md. Zafrul Hossain
MBBS, BCS (Health)
Medical Officer, Upazila Health Complex
Ullapara, Sirajganj

Soon our officials will be visiting you with a token of our appreciation

Test Yourself — TEST YOURSELF 17

1. All the points mentioned below are correct for fever except:
a. A feverish child should be assessed immediately if the child is 2-4 month old.
b. In case of fever extra fluids intake should be encouraged.
c. Penicillin especially amoxicillin or ampicillin should be avoided is young patients with sore throats.
d. Paracetamol should always be given at least 60 minutes prior to body sponging.

2. The following features are true for Graves' Disease except:
a. This is the most common cause of spontaneous thyrotoxicosis.
b. It is an autoimmune disease and is influenced by genetic factors only.
c. Smoking has been implicated in the worsening of Graves' ophthalmopathy.
d. Tremors, psychosis, nervousness are the neuromuscular features of Graves' disease.

3. All the followings are the possible causes of sudden chest pain except:
a. Angina
b. Chest infection
c. Pneumothorax
d. Arrhythmias

4. All the following points are true for Meconium Aspiration Syndrome (MAS) except:
a. MAS is exclusively a disease of newborns.
b. Incidence of MAS is higher in developed countries.
c. Pre-eclampsia is one of the definitive etiologies of MAS.
d. Presence of meconium in amniotic fluid is essential for initiating pathogenesis.

5. All the following are the diagnostic tests performed for chest pain except:
a. Stress tests
b. Electron beam computerized tomography(EBCT).
c. Magnetic Resonance Imaging(MRI)
d. Ultrasonogram.

6. All the following points are true for the diagnosis of Graves' disease except:
a. Diagnosis of hyperthyroidism requires three steps.
b. Biochemical diagnosis of thyrotoxicosis requires combination of suppressed TSH levels and elevated hormone concentrations.
c. Borderline suppression of TSH, coupled with markedly elevated T4 values is common with overt Graves' disease.
d. Total T4 values in excess of 12micrograms/ dl provides supportive evidence for thyrotoxicosis.

ROVIPHARM, Vietnam and SQUARE Pharmaceuticals Ltd., Bangladesh recently signed an agreement for export of SQUARE's products to Vietnam. Managing Director and high officials of SQUARE were present with General Director and Marketing Director of ROVIPHARM.

Mr. A L Yatawara, Managing Director, Mr. Rajiv Nanayakkara, Director and other officials of Mackwoods Healthcare Pvt. Ltd. - SQUARE's marketing partner in Sri Lanka, recently visited SQUARE Pharmaceuticals Ltd., Dhaka Unit.

Delegation from Dept. of Medical Services, Drugs, Vaccines & Equipment Division, Ministry of Health of Royal Govt. of Bhutan visited SQUARE Pharmaceuticals' formulation plant at Dhaka.

Quality Control Manager (Microbiology) of SQUARE Pharmaceuticals Ltd., Pabna Unit, is briefing SQUARE's marketing partner from Mauritius.

Production Manager of SQUARE Pharmaceuticals Ltd., Dhaka Unit, is briefing the delegates from Kazakhstan during their recent tour.

Cholesterol-lowering Drugs May Reduce Glaucoma Risk

Long-term use of cholesterol-lowering treatments, including statins, may be associated with a reduced risk of glaucoma among patients with cardiovascular disease, show results of a population-based study published in the Archives of Ophthalmology (June, p 822). The researchers, from the University of Alabama, Birmingham, used data from the medical records of 667 men aged 50 or older with a new diagnosis of glaucoma between January 1st, 1997, and December 31st, 2001. These were compared with 6,667 control patients, using prescription records to search for cholesterol lowering drug use. Statin use for 24 months or more significantly reduced risk of glaucoma (odds ratio, 0.60; 95% cl, 0.39-0.92), as did the use of non-statin cholesterol-lowering drugs (odds ratio, 0.59; 95% cl, 0.37-0.97). However, more work is needed to find out whether these treatments may provide additional therapy for glaucoma, the researchers say.

Source: www.scrippharma.com

Fast Oral HIV Test

A new rapid oral HIV test would help to widely expand AIDS screening. The test samples saliva from a subject's mouth and can offer results in as little as 20 minutes. Officials said that the kit, called the OraQuick Rapid hiv-1/2 Antibody Test, could greatly cut down on the number of people who get tested for HIV but never return days later for laboratory results.

Approximately 25% of the 900,000 Americans with HIV don't know they have the virus, according to Department of Health and Human Services data. Meanwhile, as many as 30% of people who get tested for HIV never return to hear their results. Users swab their gums and insert the swab into a vial of solution. Reddish-purple lines in small window on the kit indicate the presence of antibodies to the HIV-1strain 20 minutes later.

HIV-1 is the strain that causes most infections in the U.S. The researcher says that based on "limited" data the test can detect HIV antibodies in 99.3% of infected people. The test also avoids falsely identifying a negative person as infected 99.8% of the time.

"It's only early diagnosis that allows treatment to take place at an early and effective time" the researcher says.

Source: WebMD Medical March 26, 2004

Vitamin B_{12} Keeps the Memory in Play

The key finding in a new Swedish study shows gene and nutrition interact to contribute to cognitive problems in old age.

Scientists have known of a gene associated with higher risk for Alzheimer's disease, and they have also known that low levels of vitamin B_{12} and folate are risk factors for memory loss and Alzheimer's. However, they say this is the first study to look at the combined effect of inborn traits and environmental factors on memory.

The predisposition to Alzheimer's is found in a version of the APOE gene. Fifteen percent of the population are carriers of this genotype and have, on average, a smaller brain area associated with memory. Researchers studied 167 healthy people of average age 83 to look at the effect of a B_{12} deficiency.

During the memory test, carriers of the high-risk genotype with normal levels of B_{12} recalled a greater number of words. The high-risk genotype/ low B_{12} level group had a significant association with poorer memory. Also, having five seconds to look at and remember the words rather than two seconds created greater recall, especially in the high-risk genotype/low B_{12} level group.

Ten percent of adults aged 75 and older have low B_{12} or folate. "High-risk genotype carriers may derive relatively greater cognitive benefits from B_{12} and folate supplements. Supplement is relatively inexpensive and may be required as part of preventive health regimes for older persons,"conclude authors.

Source: Ivanhoe.com

Beta Blockers May Prevent Postoperative Heart Attacks

Beta blockers may prevent post-operative heart attacks in higher-risk patients, according to results of a new study.

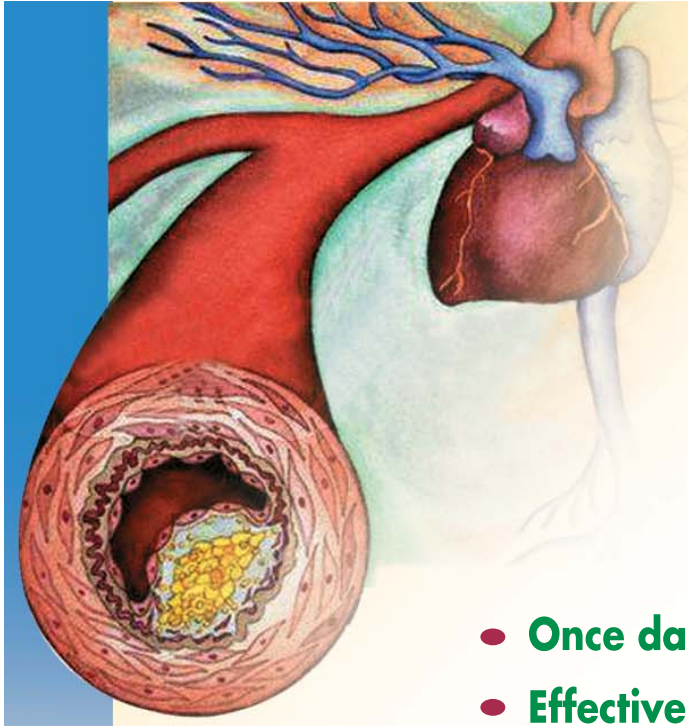
Researchers determined that patients who developed postoperative heart attack could have been identified as being at higher risk for cardiac complications.

Advances in surgical techniques, particularly as they relate to open-heart procedures, have made many procedures fairly commonplace, which may increase in older people and/or those with other serious medical conditions prior to surgery. About 5 to 10 percent of patients experience heart attack, stroke or other complications during or shortly following open-heart surgery.

In a study it is found that a large percentage of postoperative heart attacks might have been prevented had beta-blocker medication been given to higher-risk patients around the time of surgery.

The researchers also noted that using beta-blockers prior to a heart attack may reduce overall mortality, even among patients who go on to have a coronary event.

Source: Heartcenteronline, April 2004.



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