December 2019 Vol 26 No. 3 ISSN 1681-5552

Since 1993

the SQUARE Healthcare bulletin

- Hepatitis E
- COPD
- Acute Rheumatic Fever
- Ovarian Cancer

Be a Winner!

Test yourself 51

www.squarepharma.com.bd/medical-periodicals.php

Published as a service to medical professionals by

SQUARE PHARMACEUTICALS LTD. BANGLADESH

the SQUARE
healthcare bulletin

Contents

December 2019 VOL 26 NO. 3

Editorial

Dear Doctor,

Happy New Year 2020!

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

In this issue, we have a feature on "Hepatitis E" which is most common in developing countries with inadequate water supply and environmental sanitation. Large hepatitis E epidemics have been reported in Asia, the Middle East, Africa, and Central America. We have focused on "Chronic Obstructive Pulmonary Disease (COPD)", a disorder that is usually progressive, characterized by airflow limitation that is not fully reversible. Around 90% of cases of COPD are caused by cigarette smoking. We also bring you the details on "Acute Rheumatic Fever", caused by an autoimmune response to throat infection with *Streptococcus pyogenes*. Poverty and household overcrowding are associated with an increased prevalence of acute rheumatic fever and rheumatic heart disease, both of which remain a public health problem in many low-income countries. Moreover, we have included a topic on "Ovarian Cancer", which is one of the most common gynecologic cancers that has the highest mortality rate.

We believe that you will find this issue informative and interesting as well!

Wishing all of you a New Year filled with love, joy and prosperity!

Thank you!

Omar Akramur Rab

ISSN 1681-5552
Key title: the *SQUARE* (Dhaka)
Abbreviated key title: *SQUARE* (Dhaka)

Hepatitis E

Hepatitis E is a liver disease caused by the hepatitis E virus (HEV). The virus has at least 4 different types: genotypes 1, 2, 3 and 4. Genotypes 1 and 2 have been found only in humans. Genotypes 3 and 4 circulate in several animals (including pigs, wild boars and deer) without causing any disease and occasionally infect humans.

The virus is shed in the stools of infected persons and enters the human body through the intestine. It is transmitted mainly through contaminated drinking water. Usually the infection is self-limiting and resolves within 2–6 weeks. Occasionally a serious disease, known as fulminant hepatitis (acute liver failure) develops and a proportion of people with this disease can die.

The hepatitis E virus (HEV) genome contains three open reading frames (ORFs). The largest ORF-1, codes for the nonstructural proteins responsible for viral replication. ORF-2 contains genes encoding the capsid. The function of ORF-3 is unknown, but the antibodies directed against ORF-3 epitopes have been identified.

Hepatitis E results from HEV infection and is spread by fecally contaminated water within endemic areas. However, in nonendemic areas, the major mode of the spread of HEV is foodborne, especially consumption of undercooked pork, raw liver and sausages.

HEV is an RNA virus of the genus Hepevirus. It was discovered during electron microscopy of feces contaminated with enteric non-A, non-B hepatitis. The virus is icosahedral and nonenveloped. It has a diameter of approximately 34 nanometers and it contains a single strand of RNA approximately 7.5 kilobases in length. Five HEV genotypes have been identified. Genotypes 1 and 2 are considered human viruses; genotypes 3 and 4 are zoonotic and have been isolated from humans and animals (eg, pigs, boars, deer) and genotype 7 primarily infects dromedaries (single-humped camel).

HEV was discovered in the early 1980s. At that time, Soviet troops in Afghanistan were affected by large outbreaks of unexplained hepatitis (testing negative for hepatitis A virus [HAV] and hepatitis B virus [HBV]). A pooled sample of affected soldiers' stool was ingested by a Russian scientist & developed a brisk hepatitis and a new virus was found in his stool by electron microscopy. Subsequently the viral genome was cloned

and named HEV.

Epidemiology

United States statistics

Population-based surveys from 1988-1994 indicate that 21% of US adults had anti-hepatitis E virus (HEV) antibody, a rate lower than that of anti–hepatitis A virus antibody (38.3%) but higher than that of antibodies against hepatitis B (5.7%) or hepatitis C (2%).

Anti-HEV antibody rates increased markedly with age, from less than 10% among persons aged 6-19 years to more than 40% among those older than 60 years. Age-adjusted rates of anti-HEV antibody were lower among blacks (14.5%) than among non-Hispanic whites (22.1%); among men who had sex with men (23.1%) than among those who did not (23.9%); among cocaine users (16.8%) than among nonusers (23.6%); and among people living in the Southern United States (14.7%) than among people living in the Northeast (20.8%), Midwest (26.6%) or West (25%). Rates of anti-HEV antibody were minimally higher among men than among women (21.6% vs 20.4%). Among men who had sex with men, the rates of anti-HEV antibody were lower among men with HIV infection (12.8%) than among men without HIV infection (19.2%).

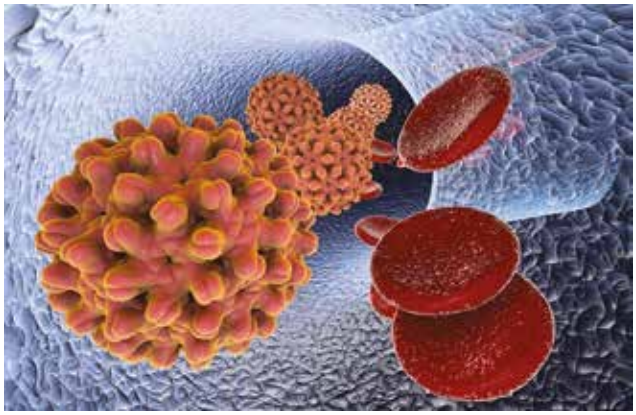
The route of exposure is unknown but is generally attributed to travel in endemic areas such as China, Nepal, India, Southwest France, North African countries and Borneo. Exposure to pigs and consumption of undercooked pork are other methods of spread in autochthonous (nonendemic) areas, as testing of samples of pig liver and sausage from commercial groceries in the United States identified HEV RNA in a high percentage of samples.

International statistics

The global disease burden of hepatitis E has been reported to be at least 20 million cases/year with 70,000 fatalities and 3,000 stillbirths. Hepatitis E has worldwide distribution, but predominating factors include tropical climates, inadequate

sanitation and poor personal hygiene. It is found most often in developing countries near the equator, in both the Eastern and Western hemispheres. Regions with a prevalence rate of more than 25% include Central America, the Middle East and large parts of Africa and Asia. Outbreaks are associated with rainy seasons, floods and overcrowding.

Water supply contamination with human feces is a frequent source of epidemics. The largest outbreak was reported in Northeast China, with 100,000 people affected between 1986 and 1988. The reservoir of HEV is unknown, but it is believed that the virus may be transmitted by animals. Waterborne epidemics of hepatitis E mainly affect young adults, the clinical attack rate being highest among those aged 15-35 years. Men are clinically infected 2-5 times more commonly than women in most outbreaks. However, no sex difference exists in exposure to HEV.



Transmission

The hepatitis E virus is transmitted mainly through the fecal-oral route due to fecal contamination of drinking water. This route accounts for a very large proportion of clinical cases with this disease. The risk factors for hepatitis E are related to poor sanitation, allowing virus excreted in the faeces of infected people to reach drinking water supplies.

Other routes of transmission have been identified, but appear to account for a much smaller number of clinical cases. These routes of transmission include:

- Ingestion of undercooked meat or meat products derived from infected animals (e.g. pork liver);
- Transfusion of infected blood products and
- Vertical transmission from a pregnant woman to her baby.

Symptoms

The incubation period following exposure to HEV ranges from 2 to 10 weeks, with an average of 5 to 6 weeks. The infected persons excrete the virus beginning from a few days before to 3-4 weeks after onset of the disease.

In areas with high disease endemicity, symptomatic infection is most common in young adults aged 15–40 years. In these areas, although infection does occur in children, they often have either no symptoms or only a mild illness without jaundice which goes undiagnosed.

Typical signs and symptoms of hepatitis include:

- An initial phase of mild fever, anorexia, nausea and vomiting, lasting for a few days; some persons may also have abdominal pain, itching (without skin lesions), skin rash or joint pain.
- Jaundice with dark urine and pale stools; and
- Hepatomegaly.

These symptoms are often indistinguishable from those experienced during other liver illnesses and typically last 1-6 weeks.

In rare cases, acute hepatitis E can be severe and result in fulminant hepatitis (acute liver failure); these patients are at risk of death.

Cases of chronic hepatitis E infection have been reported in immunosuppressed people, particularly organ transplant recipients on immunosuppressive drugs, with genotype 3 or 4 HEV infection. These remain uncommon.

HEV Infection and Pregnancy

Numerous studies from developing countries have shown excess mortality in pregnant females who develop hepatitis E virus infection. The mortality is 20 to 25% and usually occurs in the third trimester. Pregnant women die of obstetric problems, including hemorrhage or eclampsia or develop fulminant hepatic failure. Stillbirths are common, as is vertical transmission to infants who survive, who have an increased neonatal morbidity and mortality. The excess mortality in pregnancy with HEV genotypes

1 and 2 is unique. It is not seen with genotypes 3 and 4, although there have been a few documented cases in pregnant females , nor is it seen with other hepatotropic viruses.

The cause of excess maternal mortality in patients with hepatitis E virus infection is uncertain and has been the subject of many studies and much debate. Pregnancy is characterized by a state of maternal immune tolerance toward the fetus. T-cell activity is reduced, there is a reduction in cytokine production in the first 20 weeks, Th2 (T helper 2) responses predominate and immunological changes in the placenta down regulate antigen presentation. The changes in maternal immunological responses are driven, at least in part, by significant changes in hormone profiles, with increased levels of progesterone, estrogen and human chorionic gonadotropin. Studies have shown significant differences in immunological and hormonal responses in pregnant women with fulminant hepatic failure caused by hepatitis E. Finally, recent studies showed that among women infected with HEV, higher viral loads were observed in pregnant women than in women who were not pregnant.

Diagnosis

Cases of hepatitis E are not clinically distinguishable from other types of acute viral hepatitis. However, diagnosis can often be strongly suspected in appropriate epidemiologic settings, for example when several cases occur in localities in known disease-endemic areas or in settings with risk of water contamination, when the disease is more severe in pregnant women or if hepatitis A has been excluded.

Table : Epidemiology & clinical features of HEV infection in developing and developed countries

	Description or value	
Feature	**HEV in developing countries**	**HEV in developed countries**
Epidemiology		
Genotypes	1 and 2	3 and 4
Source of infection	Human	Zoonotic; pigs are primary host[a]
Route of infection	Fecal-oral via infected water	Fecal-oral via infected pig meat, direct exposure, infected water
Transfusion-related infection	Yes	Yes
Seroprevalence	Low in children of < 15 yr, increases rapidly from ages 15 to 30 yr	Steady increase throughout age groups
Incidence	Variable: 64/1,000 patient-yr, Bangladesh	Variable: 3/100 patient-yr, South of France; 7/1,000 patient-yr, USA
Outbreaks	Yes; can involve thousands of cases	No; occasional small case clusters from a food point source
Attack rate	~ 1 in 2	67-98% of those infected are asymptomatic
Person-to-person spread	Very limited	No
Seasonality	Yes; outbreaks occur at times of flooding/monsoon	No
Disease in travelers returning from areas of endemicity	Well described	Is beginning to emerge as high-risk areas become defined
Clinical features		
Age at infection (yr)	15-30	>50
Sex (male/female ratio)	2:1	>3:1
Clinical course	Self-limiting hepatitis in most	Self-limiting hepatitis in most
Neurological complications	Yes	Yes
Deaths in pregnant females	Yes; 20-25% in final trimester[b]	No
Outcome in patients with underlying chronic liver disease	Poor	Poor
Chronic infection	No	Yes; genotype 3 only
Burden of disease	3.4 million cases/yr, 70,000 deaths, 3,000 stillbirths'	Unknown

[a] HEV genotypes 3 and 4 have also been transmitted from human to human via infected blood products.

[b] The epidemiology and clinical course ofHEV genotype 1 in Egypt are significantly different from those in other developing countries. In Egypt, the seroprevalence is similar to that of HAV, with nearly universal exposure in childhood, and the risks to pregnant females maybe less. The reason for these observations is unknown.

[c] Data are for 9 of 21 regions defined for the Global Burden of Diseases, Injuries, and Risk Factors Study (the GBD 2010 Study),which represent 71% of the world,s population

Elevation in the serum aminotransferase levels is the laboratory hallmark of acute viral hepatitis. Serum alanine aminotransferase (ALT) level is usually higher than the serum aspartate aminotransferase (AST) level. The levels of aminotransferases may range from 10 times the upper limit of normal to more than 20 times the upper limit of normal. They increase rapidly and peak within 4-6 weeks of onset but generally return to normal within 1-2 months after the peak severity of the disease has passed. The serum alkaline phosphatase level may be normal or slightly increased (< 3 times upper limit of normal).

Serum bilirubin level usually ranges from 5-20 mg/dL, depending on the extent of hepatocyte damage. The patient may develop leukopenia with neutropenia or lymphopenia. Prolonged prothrombin time, decreased serum albumin and very high bilirubin are signs of impending hepatic failure requiring referral to a liver transplantation center.

Perform blood cultures if the patient is febrile and hypotensive with an elevated white blood cell (WBC) count.

Obtain serum acetaminophen levels if overdose is suspected.

Definitive diagnosis of hepatitis E infection is usually based on the detection of specific IgM antibodies to the virus in a person's blood; this is usually adequate in areas where disease is common. Rapid tests are available for field use.

Additional tests include reverse transcriptase polymerase chain reaction (RT-PCR) to detect the hepatitis E virus RNA in blood and/or stool; this assay requires specialized laboratory facilities. This test is particularly needed in areas where hepatitis E is infrequent and in cases with chronic HEV infection.

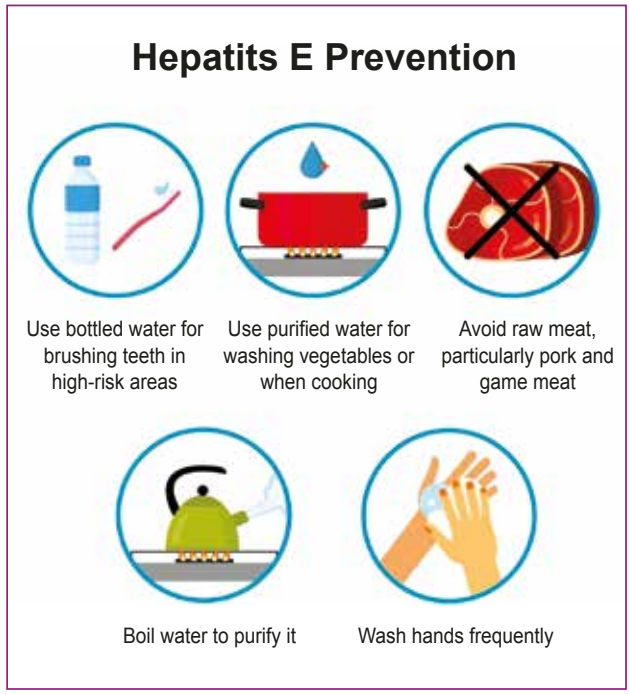
Differential Diagnosis

- Hepatitis A
- Hepatitis B
- Hepatitis C
- Hepatitis D
- Liver injury due to drugs
- Viral Hepatitis

Medical Management

Prevention

Management should be predominantly preventive, relying on clean drinking water, good sanitation and proper personal hygiene. Travelers to endemic areas should avoid drinking water or other beverages that may be contaminated and should avoid eating uncooked shellfish.



Care should be taken in the preparation of uncooked fruits or vegetables. Boiling water may prevent infection, but the effectiveness of chlorination is unknown.

Hepatitis E is preventable by vaccination. Studies in Nepal and China have shown 95% efficacy of a recombinant genotype 1 HEV vaccine in preventing infection and clinical disease. Not only did the vaccine prevent the genotype 1 HEV infection, genotype 4 HEV was also prevented with the vaccination, indicating cross-protection against different HEV genotypes. At this time, the vaccine efficacy against HEV genotype 3 is not known. A vaccine developed from HEV genotype 1 HEV vaccine was approved in China in December 2011.

A study showed long-term efficacy of this vaccine, as it induced a sustained level of antibodies and protection against hepatitis E for up to 4.5 years.

However, further evaluation of these vaccines is required to determine their efficacy in special risk groups, such as patients with end-stage liver disease or immunosuppressed individuals, to define the anti-HEV titers that can be considered protective and to know the duration of their protective effect.

Treatment of acute HEV infection

Acute hepatitis E in immunocompetent persons usually only requires symptomatic treatment, as almost all of them are able to clear the virus spontaneously. A report showed significant improvement of liver enzymes and functions in a patient with severe acute hepatitis E who was treated with ribavirin for 21 days. Although ribavirin therapy is contraindicated in pregnancy owing to teratogenicity, the risks of untreated HEV to the mother and fetus are high and trials of antiviral therapy might be worthwhile.

Treatment of chronic HEV infection

In transplant recipients with chronic HEV infection, viral clearance is desirable. The first step is to reduce the immunosuppressive therapy, as reduction of immunosuppression results in viral clearance in 30% of patients. Calcineurin inhibitor (cyclosporine A, tacrolimus) and mTOR inhibitors (rapamycin, everolimus) have an in vitro effect of stimulation of HEV replication. However, mycophenolic acid (including prodrug mycophenolate mofetil) inhibits the HEV replication in vitro.

Steroids were found not to influence HEV replication in vitro.

Antiviral therapy should be considered for patients for whom immunosuppressive therapy cannot be reduced and for those who do not achieve viral clearance after reducing immunosuppression. Although data are limited, ribavirin monotherapy (600–1000 mg/day) for at least 3 months seems to be the first treatment option for patients with chronic hepatitis E who are not able to clear HEV after immunosuppression is reduced. However, the presence of G1634 mutation in the RdRp domain of HEV ORF1 protein was reported to be associated with ribavirin treatment failure. In this situation, pegylated interferon alfa may be used as an alternative treatment option if there is no contraindication. It appears that ribavirin causes HEV mutagenesis in treated patients and distinct mutants within the viral population occur during ribavirin therapy.

Treatment with pegylated interferon alfa for 3-12 months has led to sustained clearance of HEV RNA in patients with chronic hepatitis E who underwent liver transplantation. However, interferon therapy can cause significant adverse effects and organ rejection in transplant recipients, especially those who have undergone heart or kidney transplantation.

Prognosis

No chronic cases of acute hepatitis E have been reported. The infection is self-limited. Whether protective immunoglobulins develop against future reinfection remains unknown. The overall case fatality rate is 4%.

Among pregnant women, the case fatality rate is 20% and this rate increases during the second and third trimesters. Reported causes of death include encephalopathy and disseminated intravascular coagulation. The rate of fulminant hepatic failure in infected pregnant women is high.

In a 3-year (2010-2013) prospective observational study of 55 symptomatic anti-HEV IgM-positive Indian women, the overall maternal mortality was 5%, including one antenatal death. The most common fetal complications were prematurity (80%) and premature rupture of membranes (11%), with a 28% rate of vertical transmission.

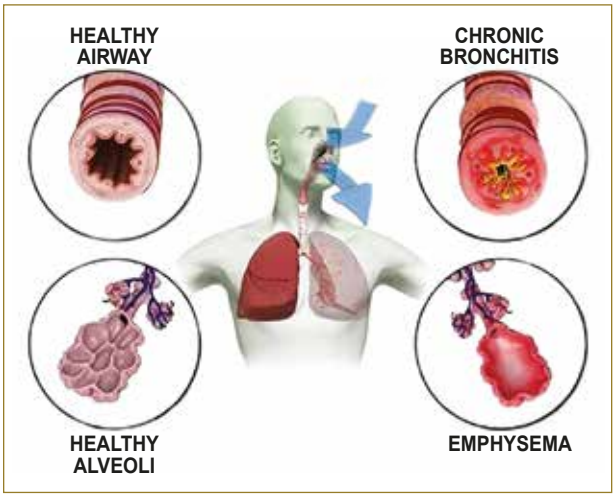
Liver transplant recipients may be at a greater risk for hepatitis E virus (HEV) infection, which can lead to chronic hepatitis and rapid progression of liver fibrosis. The presence of anti-HEV-IgG titer in pretransplantation measurements do not lead to protection of hepatitis E in postransplantation patients.

References

- https://emedicine.medscape.com/article/178140
- World Health Organisation
- Clinical Microbiology Reviews p. 116 - 138

Chronic obstructive pulmonary disease (COPD) has been a major public health problem during the 20th century and will remain a challenge for the foreseeable future. Worldwide, COPD is in the spotlight, because its high prevalence, morbidity and mortality create formidable challenges for healthcare systems.

COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.



Epidemiology

COPD is currently the fourth leading cause of death in the world. COPD is projected to be the 3rd leading cause of death by 2020. More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally. Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population. Estimated 384 million COPD cases in 2010 & global prevalence of 11.7%. With increasing prevalence of smoking in developing countries and aging populations in high-income countries, the prevalence of COPD is expected to rise over the next 30 years. By 2030 predicted 4.5 million COPD related deaths annually.

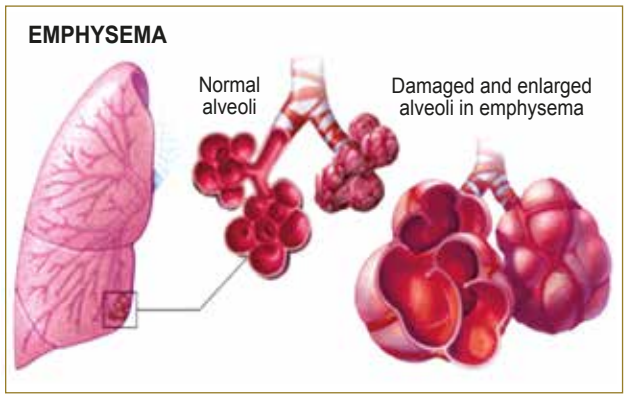
COPD has a chronic long-lasting course characterized by irreversible decline of forced expiratory volume in one second (FEV1), increasing presence of dyspnea and other respiratory symptoms and progressive deterioration of health status. After diagnosis the 10-yr survival rate is 50% with more than one-third of patients dying due to respiratory insufficiency. Particular genetic variants are likely to increase the susceptibility to environmental factors although little is known about which are the relevant genes. There is clear evidence about the role of the α-1-antitrypsin but the fraction of COPD Attributable to the relevant variants is only 1%. Phenotypic traits that are considered to play a role in the development of COPD include sex, with females being at a higher risk, bronchial responsiveness and atopy. There is strong causal evidence regarding the relationship between smoking and COPD with decline in FEV1 levelling off after smoking cessation. Passive smoking has been found to be associated with a small though statistically significant decline in FEV1.

Types of COPD

There are two main forms of COPD.

Emphysema : Emphysema is a lung condition that causes shortness of breath. In people with emphysema, alveoli are damaged. Over time, the inner walls of the alveoli weaken and rupture creating larger air spaces instead of many small ones. This reduces the surface area of the lungs and, in turn, the amount of oxygen that reaches to bloodstream.

When exhale, the damaged alveoli don't work properly and old air becomes trapped, leaving no room for fresh, oxygen-rich air to enter. Most people with emphysema also have chronic bronchitis.



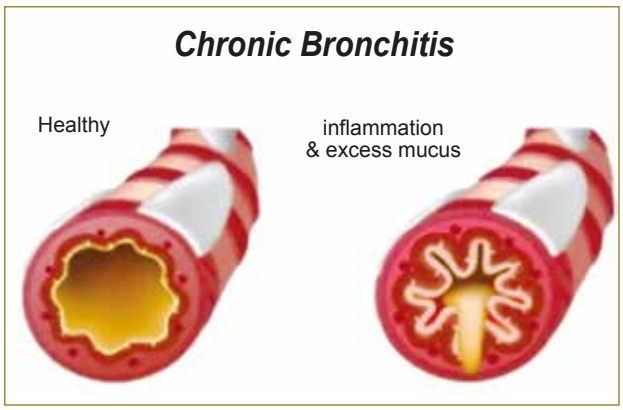
Chronic bronchitis : Chronic bronchitis, along with emphysema, is one of the lung diseases that comprise. A chronic disease, such as chronic bronchitis, is a type of condition that goes on for a

long time and does not go away but does have ups and downs in the symptoms that are present. Symptoms may get better or worse over time and there are treatments available to help control symptoms.

Chronic bronchitis should not be confused with acute bronchitis, which usually develops from a respiratory infection like a cold and goes away in a week or two. Individuals with chronic bronchitis can get an episode of acute bronchitis on top of their chronic condition. Symptoms may longer in this situation.

Key Facts about Chronic Bronchitis

- Bronchitis is a condition in which bronchial tubes, become inflamed. This irritation causes symptoms such as cough with mucus production, shortness of breath, chest discomfort and fatigue and at times wheezing. In this situation, the term asthmatic bronchitis is often used.
- To diagnose chronic (or long-lasting) bronchitis, look for a productive cough (producing mucus) that lasts at least three months and happens multiple times over the course of at least two years.



- Cigarette smoking is the major cause of chronic bronchitis. Other factors that increase risk of developing this disease include exposure to air pollution as well as dust or toxic gases in the workplace or environment. It may also occur more frequently in individuals who have a family history of bronchitis.
- Chronic bronchitis is not curable but certainly varies in the number of symptoms that are present from individual to individual. There are treatments that can help to manage the symptoms of the disease.

Causes

COPD is most common in current and former smokers. In fact, smoking accounts for up to 8 out of 10 COPD-related deaths, according to the Centers for Disease Control and Prevention (CDC). The more a person smokes, the more likely that person will develop COPD. But some people smoke for years and never get COPD. In rare cases, nonsmokers who lack a protein called alpha-1 antitrypsin can develop emphysema.

Other risk factors for COPD are:

- Exposure to certain gases or fumes in the workplace
- Exposure to heavy amounts of secondhand smoke and pollution
- Frequent use of a cooking fire without proper ventilation

Pathology

Chronic obstructive pulmonary disease (COPD) is characterized by poorly reversible airflow obstruction and an abnormal inflammatory response in the lungs. The latter represents the innate and adaptive immune responses to long term exposure to noxious particles and gases, particularly cigarette smoke. All cigarette smokers have some inflammation in their lungs, but those who develop COPD have an enhanced or abnormal response to inhaling toxic agents. This amplified response may result in mucous hyper secretion (chronic bronchitis), tissue destruction (emphysema) and disruption of normal repair and defense mechanisms causing small airway inflammation and fibrosis (bronchiolitis).

These pathological changes result in increased resistance to airflow in the small conducting airways, increased compliance of the lungs, air trapping and progressive airflow obstruction-all characteristic features of COPD. Cellular and molecular mechanisms underlying the pathological changes found in COPD.

Pathological changes found in COPD

Proximal cartilaginous airways (>2 mm in diameter)

- Increased numbers of macrophages and CD8 T lymphocytes
- Few neutrophils and eosinophils (neutrophils increase with progressive disease)
- Sub mucosal bronchial gland enlargement and goblet cell metaplasia (results in excessive mucous production or chronic bronchitis)
- Cellular infiltrates (neutrophils and lymphocytes) of bronchial glands
- Airway epithelial squamous metaplasia, ciliary dysfunction, hypertrophy of smooth muscle and connective tissue

Peripheral airways (non-cartilaginous airways <2 mm diameter)

- Increased numbers of macrophages and T lymphocytes (CD8 > CD4)
- Increased numbers of B lymphocytes, lymphoid follicles and fibroblasts
- Bronchiolitis at an early stage
- Luminal and inflammatory exudates
- Pathological extension of goblet cells and squamous metaplasia into peripheral airways
- Peri bronchial fibrosis and airway narrowing with progressive disease

Lung parenchyma (respiratory bronchioles and alveoli)

- Alveolar wall destruction from loss of epithelial and endothelial cells
- Development of emphysema
- Microscopic emphysematous changes: Centrilobular-dilatation and destruction of respiratory bronchioles (commonly found in smokers and predominantly in upper zones) Panacinar-destruction of the whole acinus (commonly found in α1 antitrypsin deficiency and more common in lower zones)
- Macroscopic emphysematous changes: Microscopic changes progress to bulla formation (defined as an emphysematous airspace > 1 cm in diameter)

Pulmonary vasculature

- Increased numbers of macrophages and T lymphocytes
- Early changes-Intimal thickening, endothelial dysfunction
- Late changes-Hypertrophy of vascular smooth muscle, collagen deposition, destruction of capillary bed, development of pulmonary hypertension and cor pulmonale

Pathophysiology of exacerbations

Exacerbations are often associated with increased neutrophilic inflammation and in some mild exacerbations, increased numbers of eosinophils. Exacerbations can be caused by infection (bacterial or viral), air pollution and changes in ambient temperature.

In mild exacerbations, airflow obstruction is unchanged or only slightly increased. Severe exacerbations are associated with worsening of pulmonary gas exchange due to increased inequality between ventilation and perfusion and subsequent respiratory muscle fatigue. The worsening ventilation-perfusion relation results from airway inflammation, oedema, mucous hyper secretion and bronchoconstriction. These reduce ventilation and cause hypoxic vasoconstriction of pulmonary arterioles, which in turn impairs perfusion.

Respiratory muscle fatigue and alveolar hypoventilation can contribute to hypoxaemia, hypercapnia and respiratory acidosis and lead to severe respiratory failure and death. Hypoxia and respiratory acidosis can induce pulmonary vasoconstriction, which increases the load on the right ventricle and, together with renal and hormonal changes, results in peripheral oedema.

Risk Factors

Smoking is the biggest risk factor for chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema. It increases the risk of both developing and dying from COPD. Approximately 85 to 90 percent of COPD cases are caused by smoking. Female smokers are nearly 13 times as likely to die from COPD as women who have never smoked; male smokers are nearly 12 times as likely to die from COPD as men who have never smoked. Other risk factors for COPD include:

- Exposure to air pollution
- Breathing second hand smoke
- Working with chemicals, dust and fumes
- A genetic condition called Alpha-1 deficiency
- A history of childhood respiratory infection

Symptoms

Symptoms may include any of the following:

- Cough, with or without mucus
- Fatigue
- Many respiratory infections
- Dyspnea that gets worse with mild activity
- Trouble catching one's breath
- Wheezing
- Because the symptoms develop slowly, some people may not know that they have COPD.

Diagnosis

- The best test for COPD is a lung function test called spirometry. Spirometry is essential for the assessment of patients with suspected chronic disease of the airways. It must be performed at either the initial or a subsequent visit, if possible before and after a trial of treatment. Early confirmation or exclusion of the diagnosis may avoid needless trials of therapy or delays in initiating other investigations. Spirometry confirms chronic airflow limitation but is of more limited value in distinguishing between asthma with fixed airflow obstruction, COPD. Measurement of peak expiratory flow (PEF), although not an alternative to spirometry, if performed repeatedly on the same meter over a period of 1–2 weeks may help to confirm the diagnosis of asthma by demonstrating excessive variability, but a normal PEF does not rule out either asthma or COPD. After the results of spirometry and other investigations are available, the provisional diagnosis from the syndrome based assessment must be reviewed and if necessary, revised. Spirometry at a single visit is not always confirmatory of a diagnosis and results must be considered in the context of the clinical presentation and whether treatment has been commenced. Inhaled corticosteroids and long-acting bronchodilators influence results, particularly if a long withhold period is not used prior to performing spirometry. Further tests might therefore be necessary either to confirm the diagnosis or to assess the response to initial and subsequent treatment.
- Imaging tests of the lungs, such as x-rays and CT scans may be ordered. With an x-ray, the lungs may look normal, even when a person has COPD. A CT scan will usually show signs of COPD.
- Sometimes, arterial blood gas may be done to measure the amounts of oxygen and carbon dioxide in the blood.

Treatment

Currently, there isn't a cure for COPD, but rescue inhalers and inhaled or oral steroids can help control symptoms. And although herbs and supplements alone can't cure or treat COPD, they can provide some symptom relief.

Pharmacological treatment:

Medical treatment:

- Bronchodilators: It open the airways
- Corticosteroids : It reduce airway inflammation
- Combination inhalers: These inhalers pair steroids with a bronchodilator
- Certain long-term antibiotics
- Roflumilast: This drug stops an enzyme called PDE4. It prevents flare-ups in people whose COPD is linked to chronic bronchitis
- Flu or pneumonia vaccines: These vaccines lower the risk for illnesses.
- Pulmonary rehabilitation: This program includes exercise, disease management and counseling to help stay as healthy and active as possible
- Oxygen therapy : It reduce shortness of breath, protect organs and enhance quality of life

Surgery:

- Bullectomy
- Lung volume reduction surgery
- Lung transplant

Vaccination:

- Influenza vaccination can reduce serious illness (such as lower respiratory tract infections requiring hospitalization) and death in COPD patients.
- Pneumococcal vaccinations, PCV13 and PPSV23, are recommended for all patients ≥ 65 years of age.

Non-pharmacological treatment:

Education & self-management:

- Addressing behavioural risk factors, including smoking cessation, maintaining or increasing physical activity and ensuring adequate sleep and a healthy diet.
- Learning to self-manage breathlessness, energy conservation techniques and stress management strategies.
- Avoiding aggravating factors, monitoring and managing worsening symptoms, having a written action plan and maintaining regular contact/communication with a healthcare professional.

Physical activity

- Pulmonary rehabilitation, including community and home-based, is an approach with clear evidence of benefits. However, the challenge is promoting physical activity and maintaining it.
- There is evidence that physical activity is decreased in COPD patients. This leads to a downward spiral of inactivity which predisposes patients to reduced quality of life, increased rates of hospitalization and mortality.
- Behaviour-targeted interventions with the aim of improving physical activity should be encouraged.

Pulmonary rehabilitation

- Patients with high symptom burden and risk of exacerbations should be encouraged to take part in a formal rehabilitation program that includes setting patient goals and is designed and delivered in a structured manner, taking into account the individual's COPD characteristics and comorbidities.
- The components of pulmonary rehabilitation may vary but evidence-based best practice for program delivery includes: structured and supervised exercise training, smoking cessation, nutrition counseling and self-management education.

Complications

- Right-sided heart failure or cor pulmonale
- Pneumonia
- Pneumothorax
- Severe weight loss and malnutrition
- Osteoporosis
- Debilitation
- Increased anxiety

Prevention

COPD is a preventable and treatable disease. Its pulmonary component is characterized by airflow limitation that is not fully reversible even with the use of bronchodilator medication. Avoiding exposures to risk factors that worsen COPD (such as cigarette smoke) are frequently employed to help manage the disease.

- To stop smoking
- To avoid secondhand smoke
- To avoid air pollution
- To avoid occupational exposures
- To be aware of other dangers such as chemicals, dust and fumes in home and at work place.
- To help fight for clean air. To work with others in community to help clean up the air.

References

- www. goldcopd.org
- www.uptodate.com
- www.medscape.com

Acute Rheumatic Fever

Acute rheumatic fever (ARF) is an autoimmune inflammatory process that develops as a sequelae of streptococcal infection. ARF has extremely variable manifestations and remains a clinical syndrome for which no specific diagnostic test exists. Persons who have experienced an episode of ARF are predisposed to recurrence following subsequent (rheumatogenic) group A streptococcal infections. The most significant complication of ARF is rheumatic heart disease, which usually occurs after repeated bouts of acute illness.

Epidemiology

The incidence of ARF has declined markedly in the past 50 years in both the United States and Western Europe. In developing countries, the magnitude of ARF is enormous. Recent estimates suggest that 33.4 million people worldwide have rheumatic heart disease and that 300,000-500,000 new cases of rheumatic fever (approximately 60% of whom will develop rheumatic heart disease) occur annually, with 230,000 deaths resulting from its complications. Almost all of this toll occurs in the developing world.

The incidence rate of rheumatic fever is as high as 50 cases per 100,000 children in many areas. Areas of hyperendemicity (eg, indigenous populations of Australia and New Zealand) see an incidence of 300-500 cases per 100,000 children, while the rates are approximately 50-fold lower in their nonindigenous compatriots. Rheumatic fever in the 21st century appears to be largely a disease of crowding and poverty. Even within developing countries with overall high rates of ARF, the segments of populations of poorer socioeconomic status and with higher rates of malnutrition suffer disproportionately.

Age

ARF is most common among children aged 5-15 years. It is relatively rare in infants and uncommon in preschool-aged children. ARF occurs in young adults, but the incidence of first episodes of ARF falls steadily after adolescence and is rare after age 35 years. The lower rate of ARF in adults may represent a decreased risk of streptococcal pharyngitis in this cohort. Recurrent episodes, with their predisposition to cause or exacerbate valvular damage, occur until middle age.

Sex

Rheumatic fever does not have a clear-cut sexual predilection, although certain clinical manifestations, such as mitral stenosis and Sydenham chorea, are more common in females who have gone through puberty.

Race

Although a genetic predisposition to ARF clearly exists, the disease does not seem to have a major racial predisposition, as it was once common in the United States and Europe and seems to decline in any locale where living conditions improve.

Mortality/Morbidity

Cardiac involvement is the most serious complication of rheumatic fever and causes significant morbidity and mortality. As stated above, about 60% of the approximately 470,000 patients diagnosed with ARF annually eventually develop carditis, joining the approximately 33 million worldwide with rheumatic heart disease. Those with rheumatic heart disease are at a high risk for additional cardiac damage with subsequent bouts of ARF and require secondary prophylaxis. Morbidity due to congestive heart failure (CHF), strokes and endocarditis is common among individuals with rheumatic heart disease and about 1-1.5% of persons with rheumatic carditis die of the disease annually.

Causes

Group A beta-hemolytic streptococcal infection may lead to rheumatic fever. The overall attack rate after streptococcal pharyngitis 0.3-3%, but certain genetically predisposed individuals, comprising perhaps 3%-6% of the population, account for those who develop rheumatic fever. Studies in developed countries have established that rheumatic fever followed only pharyngeal infections and that not all serotypes of group A streptococci cause rheumatic fever.

For example, some strains (e.g. M types 4, 2, 12) in a population susceptible to rheumatic disease do not result in recurrences of rheumatic fever. The classic rheumatogenic serotypes are thought to include 3, 5, 6, 14, 18, 19 and 24. More recent data, largely from studies of the indigenous peoples of Australia, suggest that skin infections (pyoderma) can predispose to ARF and that various other serotypes may be involved.

Two basic theories have been postulated to explain the development of ARF and its sequelae following group A streptococcal infection: (1) a toxic effect produced by an extracellular toxin of group A streptococci on target organs such as the myocardium, valves, synovium and brain and (2) an abnormal immune response to streptococcal components. Increasing and compelling evidence now strongly favors the autoimmune explanation.

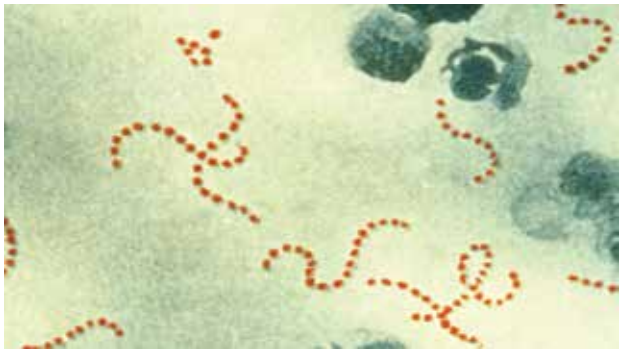


Figure: Group A Beta-hemolytic Streptococcus

Pathophysiology

ARF is characterized by nonsuppurative inflammatory lesions of the joints, heart, subcutaneous tissue and central nervous system. In developed countries, rheumatic fever follows pharyngeal infection with rheumatogenic group A streptococci.The risk of developing rheumatic fever after an episode of streptococcal pharyngitis has been estimated at 0.3-3%.

Molecular mimicry accounts for the tissue injury that occurs in rheumatic fever. Both the humoral and cellular host defenses of a genetically vulnerable host are involved. In this process, the patient's immune responses (both B- and T-cell mediated) are unable to distinguish between the invading microbe and certain host tissues. T helper 1 and cytokine Th17 appear to be key mediators of rheumatic heart disease. The resultant inflammation may persist well beyond the acute infection and produces the manifestations of rheumatic fever.

Risk Factors

Factors that can increase the risk of rheumatic fever include:

Family history : Some people carry a gene or genes that might make them more likely to develop rheumatic fever.

Type of strep bacteria : Certain strains of strep bacteria are more likely to contribute to rheumatic fever than are other strains.

Environmental factors : A greater risk of rheumatic fever is associated with overcrowding, poor sanitation and other conditions that can easily result in the rapid transmission or multiple exposures to strep bacteria.

Clinical Features

Sore throat

Although estimates vary, only 35%-60% of patients with rheumatic fever recall having any upper respiratory symptoms in the preceding several weeks. Many symptomatic individuals do not seek medical attention, go undiagnosed or do not take the prescribed antibiotic for acute rheumatic fever (ARF) prevention. If a course of penicillin or another appropriate antibiotic is taken at this time, the risk of ARF is reduced by approximately 80%.

Arthritis

Overall, arthritis occurs in approximately 75% of first attacks of ARF. The likelihood increases with the age of the patient and arthritis is a major manifestation of ARF in 92% of adults. The arthritis is typically polyarticular, but monoarthritis may occur with ARF in select high-risk populations. The arthritis of ARF is usually symmetrical and involves large joints, such as the knees, ankles, elbows and wrists. Tenosynovitis is common in adults and may be severe enough to suggest a diagnosis of disseminated gonococcal disease. Aseptic monoarticular arthritis is seen in a substantial minority of cases from higher-risk areas, especially South Asia and Oceania and can occur when NSAIDs are used early in the course. The evolution of polyarthritis in individual joints tends to overlap; therefore, multiple joints may be inflamed simultaneously, causing more of an additive than a migratory pattern. In most instances, the entire bout of arthritis subsides within 4-6 weeks without any permanent damage. If not, a different diagnosis should be entertained.

Carditis

Of first attacks of ARF, carditis occurs in 30%-60% of cases. It is more common in younger children but does occur in adults. It is usually a pancarditis

involving the pericardium, myocardium and endocardium. Severe inflammation can cause congestive heart failure (CHF). Patients with carditis may present with shortness of breath, dyspnea upon exertion, cough, paroxysmal nocturnal dyspnea, chest pain and/or orthopnea. The signs of carditis include the development of new murmurs, cardiac enlargement, CHF, pericardial friction rub and/or pericardial effusion. Carditis may also be asymptomatic and may be diagnosed solely via auscultation or echocardiography.

Sydenham chorea

This occurs in up to 25% of ARF cases in children but is very rare in adults. It is more common in girls. Sydenham chorea in ARF is likely due to molecular mimicry, with autoantibodies reacting with brain ganglioside. Sydenham chorea may occur with other symptoms or as an isolated finding. It typically presents 1-6 months after the precipitating streptococcal infection and usually has both neurologic and psychological features. The classic weakness is characterized by the inability to sustain a tetanic contraction. Patients are unable to maintain a clenched fist when attempting to grip the examiner's hand. Other findings include dysarthric speech, gait problems and poor fine-motor skills. The motor symptoms usually disappear during sleep and may be partially suppressed by sedation. In the isolated form, laboratory evidence of a preceding streptococcal infection may be lacking. Like the arthritis, Sydenham chorea usually resolves without permanent damage but occasionally lasts 2-3 years and be a major problem for the patient and her family.

Erythema marginatum

In first attacks of ARF in children, erythema marginatum occurs in approximately 10%. Like chorea, it is very rare in adults. Patients may report a nonpruritic, painless, erythematous eruption on the trunk. It is usually noted only in fair-skinned patients. The lesions may persist intermittently for weeks to months.

Subcutaneous nodules

Subcutaneous nodules are uncommon and are usually associated with severe carditis. They tend to occur several weeks after illness onset, are usually painless and usually go unnoticed by the patient. They are found primarily over the bony surfaces or prominences and in tendon sheaths. The common sites include the elbows, knees, wrists, ankles, over the Achilles tendon, the back of the scalp and spinous process of the vertebrae. They usually persist for 1-2 weeks.

Other Symptoms

Other symptoms may include fever, abdominal pain, arthralgia, malaise and epistaxis.

Laboratory Studies

No single specific laboratory test can confirm the diagnosis of acute rheumatic fever (ARF). Evidence of preceding group A streptococcal infection is an integral part of the Jones criteria for ARF diagnosis unless the patient has chorea (which may occur months after the inciting infection) or indolent rheumatic heart disease.

Throat culture

Throat culture remains the criterion standard for confirmation of group A streptococcal infection. Rapid antigen detection tests are not as sensitive. If a rapid antigen detection test result is negative, obtain a throat culture in patients with suspected rheumatic fever. On the other hand, because of the high specificity of these tests, a positive rapid antigen test confirms a streptococcal infection.

Antibody titer tests

Antibody titer tests used include ASO test, antistreptococcal DNAse B (ADB) test and the antistreptococcal hyaluronidase (AH) test.

ASO is a test used to detect streptococcal antibodies directed against streptococcal lysin O. An elevated titer is proof of a previous streptococcal infection It is usually more elevated after a pharyngeal than skin infection, while the ADB is typically elevated regardless of the site of the infection. Acute and convalescent sera, if available, are helpful for proving recent streptococcal infection. The antibody tests must be interpreted with caution in areas with high rates of streptococcal infection and ARF, as relatively high titers are commonly encountered in the population. These tests are of greater utility in areas with lower prevalence.

Acute-phase reactants

Acute-phase reactants, the erythrocyte sedimentation rate (ESR) and C-reactive protein levels (CRP) are usually elevated at the onset of ARF and serve as a minor manifestation in the Jones criteria.

Blood cultures

Blood cultures are obtained to help rule out infective endocarditis, bacteremia and disseminated gonococcal infection.

Imaging Studies

Chest radiography

Chest radiography can reveal cardiomegaly and CHF in patients with carditis.

Echocardiography

Echocardiography may demonstrate valvular regurgitant lesions in patients with ARF who do not have overt clinical manifestations of carditis. This is now considered an integral part of the evaluation of proven or suspected ARF everywhere. Patients with echocardiographically diagnosed subclinical carditis cases should receive the same long-term penicillin prophylaxis as those with the more classic clinical carditis, since they are also at risk for poor outcomes due to recurrent rheumatic heart disease. Valvular stenotic lesions, especially of the mitral valve, can be observed in rheumatic heart disease. In the absence of mitral valve disease involvement, isolated echocardiographic disease of the aortic valve is uncommon in patients with rheumatic heart disease.

Other Tests

Various other studies may be needed to rule out other illnesses in the differential diagnoses. Common tests would include rheumatoid factor, antinuclear antibody (ANA), Lyme serology, blood cultures and evaluation for gonorrhea.

Histologic Findings

Rheumatic fever is characterized pathologically by exudative and proliferative inflammatory lesions of the connective tissue in the heart, joints, blood vessels and subcutaneous tissue. In the early stage, fragmentation of collagen fibers, cellular infiltration that is predominantly lymphocytic and fibrinoid deposition followed by the appearance of a myocardial Aschoff nodule (a perivascular focus of inflammation that has an area of central necrosis surrounded by a rosette of large mononuclear and giant multinuclear cells) occur. The nuclei of these cells resemble owl eyes and are called Anichkov cells. Subcutaneous nodules histologically resemble Aschoff nodules. The brain may show scattered areas of arteritis and petechial hemorrhages, which have an uncertain relationship to Sydenham chorea.

Diagnosis

Because acute rheumatic fever (ARF) can have diverse manifestations and since no specific diagnostic test for the disease exists, arriving at the correct diagnosis is particularly important. This is essential not only in terms of prescribing appropriate therapy for the acute attack but also because of the necessity for prescribing continuous antistreptococcal prophylaxis to prevent subsequent attacks and additional damage. The Jones criteria were first established in 1944 and have been modified or updated several times, most recently in 2015.

Jones criteria

Major criteria are as follows:

- Carditis (clinical or echocardiographic diagnosis)
- Polyarthritis or monoarthritis: Polyarthralgias can be considered only after careful consideration of the differential diagnoses.
- Chorea (rare in adults)
- Erythema marginatum (uncommon; rare in adults)
- Subcutaneous nodules (uncommon; rare in adults)

Minor criteria are as follows:

- Polyarthralgia (cannot count arthritis as a major criterion and arthralgia as a minor criterion)
- Fever exceeding 38°C
- Elevated ESR (>30 mm/hr) or CRP level (>3 mg/L)
- Prolonged PR interval

Supporting evidence

Evidence of group A streptococcal disease is required for diagnosis, except when rheumatic fever is first discovered after a long latent period (eg, Sydenham chorea, indolent carditis), as follows:

- Evidence of preceding group A streptococcal infection - Positive throat culture or rapid antigen test result
- Elevated or rising streptococcal antibody titer

Scoring

If supported by evidence of preceding group A streptococcal infection, the presence of two major manifestations or one major and two minor manifestations indicates a high probability of ARF. Failure to fulfill the Jones criteria makes the diagnosis unlikely but not impossible. Clinical judgment is required. Recurrent ARF can be diagnosed based on 2 major, 1 major plus 2 minor or 3 minor criteria.

Treatment

Medical care

General treatment of the acute episode

Anti-inflammatory agents are used to control the arthritis, fever and other acute symptoms. Salicylates are the preferred agents, although other nonsteroidal agents are probably equally efficacious. Steroids are also effective but should probably be reserved for patients in whom salicylates fail, since there is a risk of rebound when they are withdrawn. Patients are typically advised to rest through the acute illness and to then gradually increase activity; Intravenous immunoglobulin has not been shown to reduce the risk of rheumatic heart disease or to substantially improve the clinical course.

Chorea is usually managed conservatively in a quiet nonstimulatory environment; valproic acid is the preferred agent if sedation is needed. Intravenous immunoglobulin, steroids and plasmapheresis have all been used successfully in refractory chorea, although conclusive evidence of their efficacy is limited.

Cardiac management

Bed rest is essential in patients with cardiac involvement. Carditis resulting in heart failure is treated with conventional measures; some use corticosteroids for severe carditis, although data to support this are scant. Diuretics and vasodilators are the mainstays of therapy.

Prophylaxis

Antibiotics

Antibiotic treatment in patients who present with acute rheumatic fever (ARF) is necessary irrespective of the throat culture result. Such therapy probably does not alter the risk of developing rheumatic heart disease but at least minimizes the possible transmission of a rheumatogenic streptococcal strain.

Primary prophylaxis (treatment of streptococcal pharyngitis) dramatically reduces the risk of ARF and should be provided whenever a group A streptococcal pharyngitis is confirmed. Treatment of pharyngitis without proof of group A streptococcal etiology may be reasonable in areas of high endemicity. Secondary prevention is recommended to prevent additional streptococcal infections and is believed by most experts to be a critical step in management of ARF. The exact duration of chronic antimicrobial prophylaxis remains controversial, but the WHO guidelines are commonly used. There had been concern that sustained benzathine penicillin as secondary prophylaxis would lead to the development of resistant strains of *Streptococcus viridans*, but a 2008 study found no support for this hypothesis.

Rheumatic fever with carditis and clinically significant residual heart disease requires antibiotic treatment for a minimum of 10 years after the latest episode; prophylaxis is required until the patient is aged at least 40-45 years and is sometimes continued for life. Rheumatic fever with carditis and no residual heart disease aside from mild mitral regurgitation requires antibiotic treatment for 10 years or until age 25 years (whichever is longer). Rheumatic fever without carditis requires antibiotic treatment for 5 years or until the patient is aged 18-21 years (whichever is longer).

Children given penicillin G benzathine at a dose of 1.2 million U IM per month, experienced a recurrence rate of 0.4 cases per 100 patient-years of observation. ARF recurrence rates have been found to be even lower if penicillin is administered once in three weeks instead of monthly. This regimen may be appropriate in patients with severe rheumatic heart disease.

Weigh the benefits of a 3-week regimen against patient compliance and cost; compliance is often poor to start with, at least partially due to the pain of the injections. Long-term administration of oral penicillin may be used in lieu of the intramuscular route. Erythromycin or sulfadiazine may be used in patients who are allergic to penicillin.

Anti-inflammatory agents

Salicylates and corticosteroids are the mainstay of the anti-inflammatory treatment of ARF. Anti-inflammatory drugs should be avoided until diagnosis is confirmed, as they may mask symptoms essential to the diagnosis. Analgesics without anti-inflammatory properties (ie, codeine) are used for mild disease. Corticosteroids and salicylates cannot prevent or modify the development of subsequent rheumatic heart disease but are used for symptomatic relief. Clinical or laboratory manifestations of rheumatic inflammation may recur upon cessation of anti- inflammatory therapy. Rebound occurs frequently with corticosteroids; hence, they require gradual tapering rather than abrupt cessation. Salicylates are usually continued for a month following corti- costeroid discontinuance.

Surgical care

Surgical care is not typically indicated in ARF. Surgical intervention is required only to treat long-term valvular cardiac sequelae of ARF that cause stenosis.

Follow-up

Patients should be closely observed until all acute symptoms have resolved and they have returned to their normal state of health. Secondary prophylaxis requires years of follow-up and is the critical step in maintaining the health of the recovered patient. Compliance with long-term secondary antibiotic prophylaxis is often poor and close follow-up is mandatory.

Prevention

Primary prophylaxis (treatment of streptococcal pharyngitis) dramatically reduces the risk of ARF and should be provided whenever possible. Secondary prophylaxis is essential in all patients with rheumatic fever. Ultimately, a vaccine will be the prevention of choice for ARF. Research on such a product is ongoing.

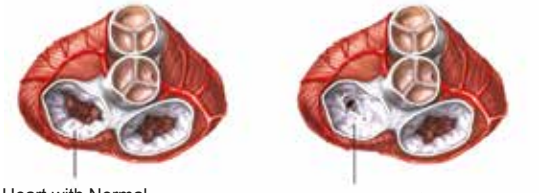
Complications

Immediate complications

Pancarditis that causes CHF, heart blocks or pericardial effusion requires emergent inpatient care and cardiology evaluation. Chorea can present months after the inciting infection and can be quite debilitating.

Long-term sequelae

The only long-term sequela is rheumatic heart disease, which can present years later as valvular stenosis, most commonly involving the mitral valve.



Heart with Normal Mitral Valve

Narrowing down of Mitral Valve
Rheumatic Mitral Valve (With Stenosis)

These patients are prone to infective endocarditis and stroke. Valvular stenosis can lead to heart failure and may require surgery.

Prognosis

The prognosis of ARF has been improved by preventing recurrent attacks with secondary antimicrobial prophylaxis. The ultimate prognosis of an individual attack is related directly to the severity of cardiac involvement during the acute phase. About 60% of patients with carditis improve over a decade; in some, murmurs disappear. However, the overall prognosis is worse in those with severe carditis at first presentation and most develop significant rheumatic heart disease. Only 6% of patients without carditis during their attack of ARF have an audible heart murmur in 10 years.

Patient Education

Patients, especially children, should receive medical attention when they develop a sore throat. Compliance with oral primary prophylaxis and secondary prophylaxis regimens is essential to prevent ARF and its sequelae.

References

- www.medscape.com
- www.medicalnewstoday.com
- The Lancet

Ovarian Cancer

Ovarian cancer is one of the most common gynecologic cancers that rank third after cervical and uterine cancer. It also has the worst prognosis and the highest mortality rate. Although ovarian cancer has a lower prevalence in comparison with breast cancer, it is three times more lethal and it is predicted that, by the year 2040, the mortality rate of this cancer will rise significantly. The high mortality rate of ovarian cancer is caused by asymptomatic and secret growth of the tumor, delayed onset of symptoms and lack of proper screening that result in its diagnosis in the advanced stages. Thus, silent killer is a name that has been given to this cancer.

Epidemiology

Ovarian cancer accounts for an estimated 239,000 new cases and 152,000 deaths worldwide annually. The highest rates (11.4 per 100,000 and 6.0 per 100,000, respectively) are seen in Eastern and Central Europe. Although China has a relatively low incidence rate (4.1 per 100,000), the large population translates to an estimated 52,100 new cases and 22,500 related deaths in 2015. In comparison, 21,290 cases and 14,180 related deaths are estimated to occur in the USA during the same year.

A woman's lifetime risk of developing ovarian cancer is 1 in 75 and chance of dying of the disease is 1 in 100. The disease typically presents at late stage when the 5-year relative survival rate is only 29%. Few cases (15%) are diagnosed with localized tumor (stage 1) when the 5-year survival rate is 92%. Strikingly, the overall 5-year relative survival rate generally ranges between 30%–40% across the globe and has seen only very modest increases (2%–4%) since 1995.

Causes and Risk Factors

The exact cause of ovarian cancer is unknown. Factors that can increase the risk:

Family history: Having a close relative with a history of ovarian or breast cancer increases a person's chance of developing ovarian cancer themselves.

Age: Around 50% of ovarian cancer cases occur after the age of 63 years.

Reproductive history: Having had one or more full term pregnancies is associated with a lower risk of ovarian cancer. The more pregnancies a woman has, the lower the risk seems to be. Breastfeeding may also lower the risk. However, having children later in life (after age 35) or never having children are associated with a higher risk. Females who use birth control pills or an injectable contraceptive hormone also appear to have a lower risk.

Breast cancer: People with a history of breast cancer seem to have a higher chance of ovarian cancer. This may be due to changes in the BRCA gene.

Hormone therapy: Undergoing hormone replacement therapy (HRT) after menopause appears to increase the risk of ovarian cancer.

Obesity and overweight: Ovarian cancer is more common in people with a body mass index (BMI) of over 30.

Gynecologic surgery: A hysterectomy, may reduce the risk of ovarian cancer by one-third.

Risk for transgender people: Having high levels of androgen may increase the risk of ovarian cancer.

Symptoms

Most ovarian cancers start in the epithelium or outer lining of the ovary. In the early stages, there may be few or no symptoms. If symptoms do occur, they can resemble those of other conditions, such as premenstrual syndrome, irritable bowel syndrome or a temporary bladder problem. However, in ovarian cancer, the symptoms will persist and worsen.

Early symptoms may include:

- Pain or pressure in the pelvis
- Unexpected vaginal bleeding
- Pain in the back or abdomen
- Bloating
- Feeling full rapidly when eating
- Changes in urination patterns, such as more frequent urination
- Changes in bowel habits, such as constipation

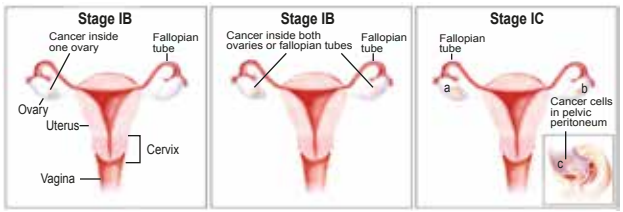
There may also be:

- Nausea and indigestion
- Appetite loss
- Weight loss
- Breathlessness
- Fatigue

The symptoms can change if the cancer spreads to other parts of the body.

Stages of Ovarian Cancer

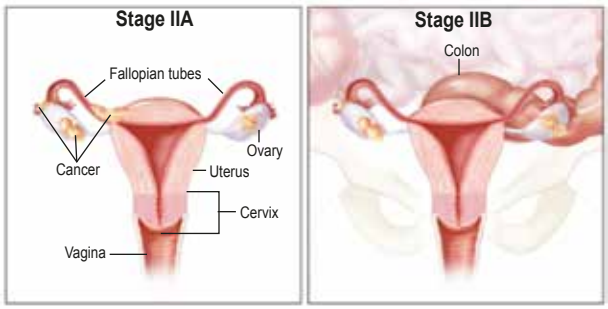
There are four stages and each stage has sub-stages:



Stage 1

Stage 1 ovarian cancer has three sub-stages:

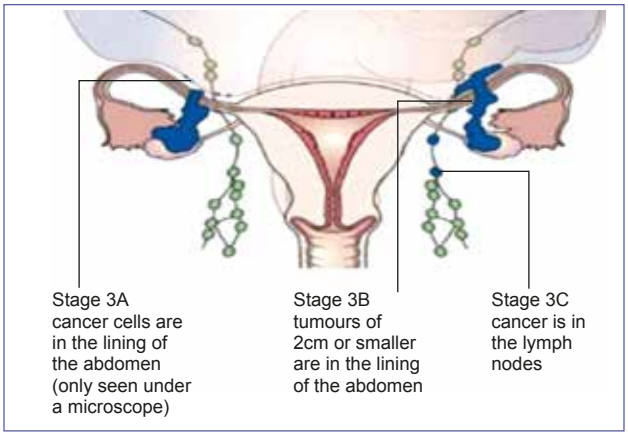
- Stage 1A: The cancer is limited or localized, to one ovary.
- Stage 1B: The cancer is in both ovaries.
- Stage 1C: There are also cancer cells on the outside of the ovary.



Stage 2

In stage 2, the tumor has spread to other pelvic structures. It has two sub-stages:

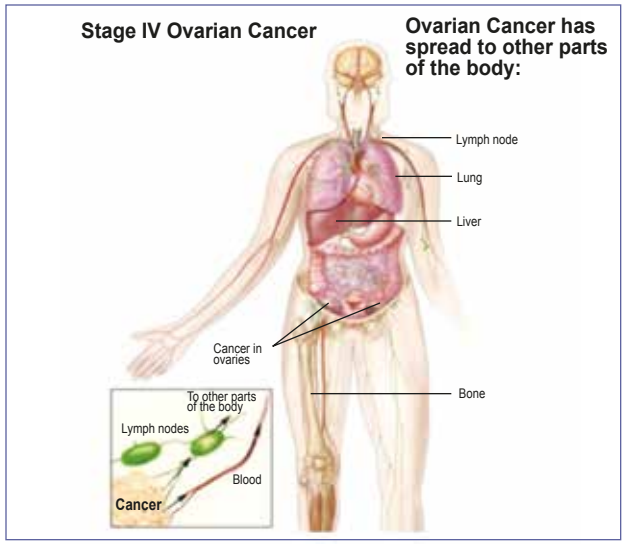
- Stage 2A: The cancer has spread to the uterus or fallopian tubes.
- Stage 2B: The cancer spread to the bladder or rectum.



Stage 3

Stage 3 ovarian cancer has three sub-stages:

- Stage 3A: The cancer has spread beyond the pelvis to the lining of the abdomen and the lymph nodes in the abdomen.
- Stage 3B: The cancer cells are outside of the spleen or liver.
- Stage 3C: Deposits of cancer at least 3/4 of an inch are seen on the abdomen or outside the spleen or liver. However, the cancer isn't inside the spleen or liver.



Stage 4

In stage 4, the tumor has metastasized or spread, beyond the pelvis, abdomen and lymph nodes to the liver or lungs. There are two sub-stages in stage 4:

- In stage 4A, the cancerous cells are in the fluid around the lungs.
- In stage 4B, the most advanced stage, the cells have reached the inside of the spleen or liver or even other distant organs like the skin or brain.

Types

There are over 30 types of ovarian cancer, depending on the type of cell in which they start. There are three common cell types:

- Epithelial cells, which occur in the lining of the surface of the ovary
- Germ cells, which will become eggs for reproduction
- Stromal cells, which release hormones and link up the structures of the ovaries

Epithelial tumors are the most common and the most invasive. They occur in around 85–90% of people with ovarian cancer.

Germ cell tumors are often benign. In 90% of cases that become cancerous, treatment is effective.

Diagnosis

If routine screening or symptoms suggest that a person may have ovarian cancer then recommended for:

Blood tests: These tests will check for high levels of a marker called CA-125.

Imaging tests: Including a transvaginal ultrasound, an MRI scan or a CT scan.

Laparoscopy: To see the ovaries and perhaps take a tissue sample for a biopsy.

Biopsy: This involves the microscopic examination of a tissue sample. Only a biopsy can confirm that a person has cancer.

Treatment

Treatment will depend on many factors, including:

- The type, stage and grade of the cancer
- The individual's age and overall health
- Their personal preferences
- Accessibility and affordability of treatment

Surgery: The choice will depend on the type of cancer and how far it has spread. Surgical options include a hysterectomy, removing one or both ovaries and removing affected lymph nodes.

Chemotherapy: These drugs aim to kill cancer cells. If a person takes chemotherapy drugs by mouth or as an injection or infusion, they will affect the whole body. Another option is intraperitoneal chemotherapy. In this case, a tube delivers the drug directly to the body area affected by cancer.

Targeted therapy: Some treatments target specific cells that help promote cancer growth. Examples include monoclonal antibody therapy and angiogenesis inhibitors. Targeted therapy aims to limit the adverse effects by targeting specific functions.

Radiation therapy: This technique uses X-rays to kills cancer cells. One way to do this is by introducing a radioactive liquid into the peritoneum. This may help people with advanced ovarian cancer.

Immunotherapy (biotherapy): This aims to boost the immune system's ability to defend the body against cancer. Vaccine therapy involves injecting substances that will find and kill a tumor. It may help people with advanced ovarian cancer.

Survival rates

The current 5 year survival rates for ovarian cancer reflect the percentage of people who lived 5 or more years after receiving a diagnosis in 2008-2014. It depends on the stage and type of the cancer. Individual factors, such as age, overall health and access to treatment, also affect survival rates.

Prevention

There are no proven ways to totally eliminate the risk of developing ovarian cancer. However, there are many steps to lower the risk. Factors that have been shown to lower risk of developing ovarian cancer include:

- Taking oral birth control pills
- Breastfeeding
- Pregnancy
- Surgical procedures on your reproductive organs (like a tubal ligation or hysterectomy)

Conclusion

All types of ovarian cancer are treatable if a person receives a diagnosis in the early stages. Some types are also highly treatable in the later stages. When considering survival statistics for ovarian cancer, it is also worth noting that medical advances have been improving the outlook over the past 20 years. Nevertheless, attending regular screening and if any symptoms appear can often lead to an early diagnosis and this will increase the chance of receiving effective treatment.

Reference:

- www.medicalnewstoday.com
- www.healthline.com
- www.ncbi.nlm.nih.gov
- International journal of women's health

Test Yourself - 50

Correct Answers :

1.	c	2.	a	3.	b	4.	a	5.	b	6.	c

CONGRATULATIONS!

WINNERS

Dr. Mohammad Moinuddin Chowdhury
FCPS (Medicine)
Asst. Prof. CMCH, Chattagram

Dr. Md. Enamul Haque Azad
MBBS, RMO
People's Hospital Ltd. Chattagram

Dr. Khaleda Akhter
MBBS, MCPS (Gynae)
Gynae Specialist
Cumilla Medical Centre, Cumilla

Dr. Begum Shaira Sharifa
DGO, MCPS, FCPS (Gynae & Obs.)
Asst. Prof. NICRH, Dhaka

Dr. Rayhan Islam Shovon
MBBS, IMO
Muksudpur UHC, Gopalganj

Dr. Afroza Begum
MBBS, DGO, BCS, FCPS, Part-I
Talukdar Clinic, Muktagacha
Mymensingh

Dr. Md. Khairul Islam
Asst. Registrar (Medicine)
Kushtia Medical College Hospital

Dr. Jubayer Hossain
MRCP
Asst. Prof., Medicine Unit -2
SBMCH, Barishal

Dr. Shahidul Islam Sikder
MBBS, FCPS, Surgery Consultant
250 Beded District Hospital
Kishoregonj

Dr. Md. Abu Masud Ansari
Asst. Registrar, Medicine Unit
TMSS Medical College Hospital
Bogura

Test Yourself - 51

1. **The followings are true for "Ovarian Cancer" except:**
   a. It has the worst prognosis and the highest mortality rate.
   b. Most ovarian cancers start in the epithelium or outer layer of the ovary.
   c. The stage 2 ovarian cancer has three sub-stages.
   d. All types of ovarian cancers are treatable if diagnosed in early stage.

2. **All the followings are correct for "COPD" except:**
   a. It is currently the fifth leading causes of death in the world.
   b. Smoking is the biggest risk factor for COPD.
   c. The best test for COPD is the spirometry.
   d. In a COPD patient, the lungs may look normal in chest x-ray.

3. **All the below are true for "Hepatitis E" except:**
   a. The incubation period following exposure to HEV ranges from 2 – 10 weeks.
   b. A vaccine developed from HEV genotype 3 has shown 95% efficacy.
   c. Acute hepatitis E in immunocompetent persons usually only requires symptomatic treatment.
   d. Among pregnant women, the case fatality rate is 20%.

4. **All the followings are correct for "Acute Rheumatic Fever" except:**
   a. In developing countries the magnitude of acute rheumatic fever is enormous.
   b. Carditis occurs in 70% - 80% of cases of first attack of acute rheumatic fever.
   c. Sydenham Chorea is very rare in adults.
   d. Subcutaneous nodules are uncommon and usually associated with severe carditis .

5. **The followings are right for "COPD" except:**
   a. Influenza vaccination can reduce serious illness and death in COPD.
   b. Spirometry confirms chronic airflow limitations and valuable in distinguishing between asthma with COPD.
   c. Bronchodilators, corticosteroids, pulmonary rehabilitation are among the medical treatment of COPD.
   d. Pneumonia, Pneumothorax, Debilitation are among the complications.

6. **All the followings are correct for "Acute Rheumatic Fever" except:**
   a. Carditis, chorea, elevated ESR are all among the major Jones Criteria.
   b. Anti-inflammatory agents are used to control the arthritis, fever and other acute symptoms.
   c. Primary prophylaxis dramatically reduces the risk of acute rheumatic fever.
   d. Rheumatic heart disease is the only long term sequela of rheumatic fever.

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

Neurolep™

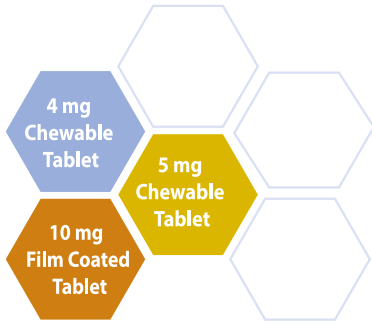
Piracetam

Tablet (800 mg)
Oral Solution (500 mg/5ml)

The Ultimate Memory Enhancer

Montene®

Montelukast USP Tablet



Once daily to prevent asthma & allergy symptoms

- First-line treatment option for persistent asthma
- Treatment of symptoms of seasonal allergic rhinitis
- Prevents exercise-induced asthma

Since 1958

SQUARE
PHARMACEUTICALS LTD.
BANGLADESH

www.squarepharma.com.bd

SQUARE

December 2019 Vol 26 No. 3 ISSN 1681-5552

Healthcare bulletin the SQUARE

Medical services department, SQUARE PHARMACEUTICALS LTD. Corporate headquarters, Square centre
48, Mohakhali Commercial Area, Dhaka- 1212, Tel: 8833047-56, 880-2-9859007 (10 lines) Fax: 880-2 882 8608 / 882 8609
Email: infosquaregroup.com, Web page; http//www.squarepharma.com.bd, Omar Akramur Rab <oar@squaregroup.com>

Designed by Creative services, PMD SQUARE PHARMACEUTICALS LTD.