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the SQUARE

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Samson H Chowdhury (1925-2012)

- *Chikungunya Fever*
- *Isolated Systolic Hypertension*
- *Rotavirus Diarrhea*
- *Chronic Lymphocytic Leukemia*

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Editorial

Dear Doctor

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

Firstly, we deeply mourn at the demise of the chairman of the *SQUARE* group Samson H Chowdhury. In the corporate world, Bangladesh will rarely find someone who has the same impact on people as him. His passing is a huge loss to the *SQUARE* family as well as the nation. His foresighted vision and dynamic leadership lead the *SQUARE* group at this height. His inspiration will definitely drive us to move forward and overcoming all the challenges to take *SQUARE* to the higher level from here.

In this edition, we have a feature on Chikungunya fever, a viral disease transmitted to humans by the bite of infected mosquitoes. We bring you all the details on Isolated Systolic Hypertension (ISH). For years, doctors focused primarily on diastolic blood pressure. The theory was that the body could tolerate occasional increases in systolic blood pressure, but consistently high diastolic pressure could lead to health problems. However, doctors now know that high systolic pressure is as important as high diastolic pressure and even more important in people older than age 50. We have presented a feature on Rotavirus which is the leading cause of severe diarrhea in infants and young children worldwide. Globally, it causes more than a half a million deaths each year in children younger than 5 years of age. Besides, we have also focused on Chronic lymphocytic leukemia (chronic lymphoid leukemia, CLL) which is a monoclonal disorder characterized by a progressive accumulation of functionally incompetent lymphocytes.

We have our regular feature on "Product profile", "*SQUARE* in International Business" and "Glimpse of MSD activities".

We extensively searched for current publications and strive to provide the latest information on those topics. We are confident that you will find this issue informative and interesting as well !

Wishing all of you, a safe, healthy and peaceful life !

Thank you !

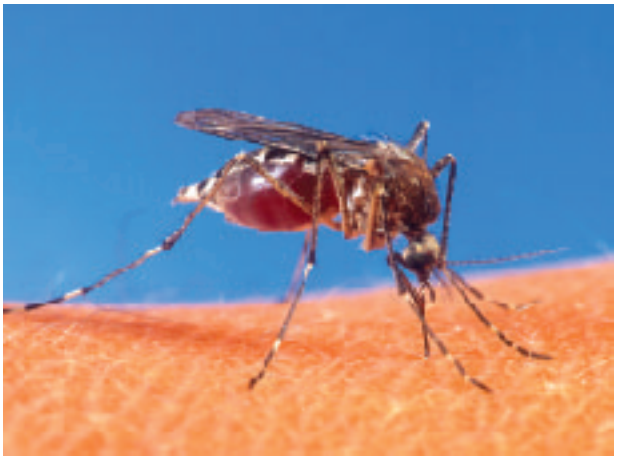
Omar Akramur Rab

ISSN 1681-5552
Key title: The square (Dhaka)
Abbreviated key title: Square (Dhaka)

The whole nation realizes that the departure of such a visionary business icon is an irrecoverable loss. We are overwhelmed and gratified to see the abundance of tributes full of compassion that have been paid on the demise of Samson H Chowdhury, the founder of Square group.

Chikungunya Fever

Chikungunya fever, is a viral illness that is spread by the bite of infected mosquitoes. The disease resembles dengue fever and is characterized by severe, sometimes persistent joint pain as well as fever and rash. It is rarely life-threatening. Nevertheless widespread occurrence of diseases causes substantial morbidity and economic loss.



Aedes aegypti

History

The name is derived from the 'Makonde language' Tanzania meaning "that which bends up" in reference to the stooped posture developed as a result of the arthritic symptoms of the disease. The disease was first described by Marion Robinson and W.H.R. Lumsden in 1955, following an outbreak in 1952 on the Makonde Plateau, along the border between Mozambique and Tanganyika (the mainland part of modern day Tanzania). Since its discovery in Tanzania, Africa in 1953, chikungunya virus outbreaks have occurred occasionally in Africa, South Asia and Southeast Asia but recent outbreaks have spread the disease over a wider range. It is an alphavirus of the family Togaviridae but recent research by the Pasteur Institute in Paris has suggested that Chikungunya virus strains in the 2005-2006 Reunion Island outbreak incurred a mutation that facilitated transmission by Aedes albopictus.

Epidemiology

Epidemics of fever, rash and arthritis, resembling Chikungunya fever have been recorded as early as 1824 in India and elsewhere. However, the virus was first isolated between 1952-1953 from both man and mosquitoes during an epidemic of fever that was considered clinically indistinguishable from dengue, in the Tanzania.

Chikungunya fever displays interesting epidemiological profiles: major epidemics appear and disappear cyclically, usually with an inter-epidemic period of 7-8 years and sometimes as long as 20 years. After a long period of absence, outbreaks of CHIK fevers have appeared in Indonesia in 1999.

Chikungunya in Asia (1960-1982)

Between 1960 and 1982, outbreaks of Chikungunya fever were reported from Africa and Asia. In Asia, virus strains have been isolated in Bangkok in 1960s; various parts of India including Vellore, Calcutta and Maharastha in 1964; in Sri Lanka in 1969; Vietnam in 1975; Myanmar in 1975 and Indonesia in 1982.

Recent occurrences of chikungunya fever

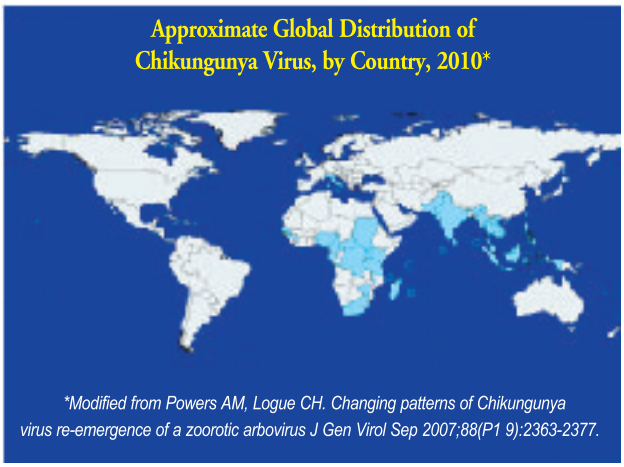
After an interval of more than 20 years, chikungunya fever has been reported from several countries including India, Indonesia, Maldives, Thailand and various Indian Ocean islands including Comoros, Mauritius, Reunion and Seychelles.

Chikungunya fever in India

Till 10 October 2006, 151 districts of eight states/provinces of India have been affected by chikungunya fever. The affected states are Andhra Pradesh, Andaman & Nicobar Islands, Tamil Nadu, Karnataka, Maharashtra, Gujarat, Madhya Pradesh, Kerala and Delhi.

More than 1.25 million cases have been reported from the country with 752,245 cases from Karnataka and 258,998 from Maharashtra provinces. In some areas attack rates have reached up to 45%.

The geographic range of chikungunya virus is mainly in Africa and Asia in 2010.

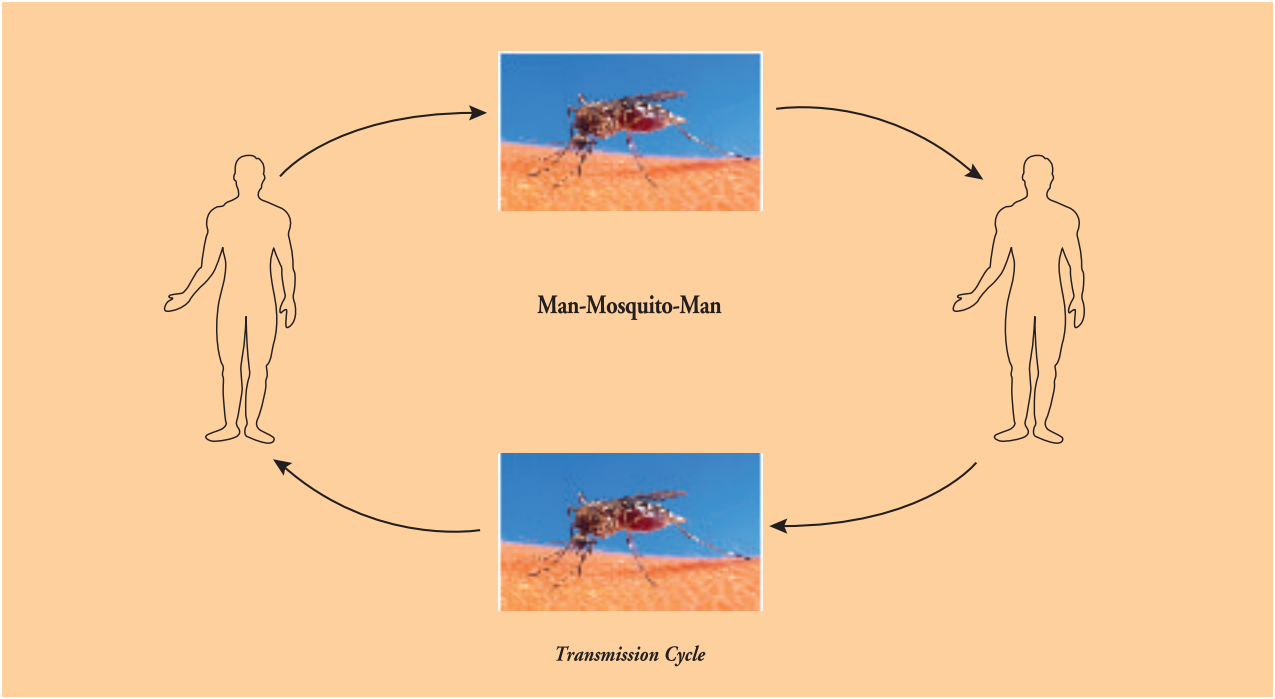


Transmission

Chikungunya is spread by the bite of an Aedes mosquito, primarily Aedes aegypti. Humans are thought to be the major source or reservoir of chikungunya virus for mosquitoes. Therefore, the mosquito usually transmits the disease by biting an infected person and then biting someone else. An infected person cannot spread the infection directly to other persons. Aedes aegypti mosquitoes bite during the day time. After the bite of an infected mosquito, onset of illness occurs usually between four and eight days but can range from 2 to 12 days.

Signs and symptoms

Chikungunya is characterized by an abrupt onset of fever frequently accompanied by joint pain. Other common signs and symptoms include muscle pain, headache, nausea, fatigue and rash. The joint pain is often very debilitating but usually ends within a few days or weeks. Most patients recover fully but in some cases joint pain may persist for several months or even years. Occasional cases of eye, neurological and heart complications have been reported,



Transmission Cycle

as well as gastrointestinal complaints. Serious complications are not common but in older people, the disease can contribute to the cause of death. Often symptoms in infected individuals are mild and the infection may go unrecognized or be misdiagnosed in areas where dengue occurs.

Chikungunya and dengue fevers

The clinical manifestations of chikungunya fever have to be distinguished from dengue fever. Co-occurrence of both fevers has been recently observed in Maharashtra state of India thus highlighting the importance of strong clinical suspicion and efficient laboratory support.

Diagnosis

Several methods can be used for diagnosis. Serological tests, such as enzyme-linked immunosorbent assays (ELISA), may confirm the presence of IgM and IgG anti-chikungunya antibodies. IgM antibody levels are highest three to five weeks after the onset of illness and persist for about two months. The virus may be isolated from the blood during the first few days of infection. Various reverse transcriptase-polymerase chain reaction (RT-PCR) methods are available but are of variable sensitivity. Some are suited to clinical diagnosis. RT-PCR products from clinical samples may also be used for genotyping of the virus, allowing comparisons with virus samples from various geographical sources.

Treatment

There is no vaccine or specific antiviral treatment currently available for chikungunya fever. Treatment is symptomatic and can include rest, fluids and medicines to relieve symptoms of fever and aching such as ibuprofen, naproxen, acetaminophen or paracetamol. Aspirin should be avoided. Infected persons should be protected from further mosquito exposure (staying indoors in areas with screens and/or under a mosquito net) during the first few days of the illness so they can not contribute to the transmission cycle.

Prevention

The best way to prevent chikungunya virus infection is to avoid mosquito bites. There is no vaccine or preventive drug currently available. Prevention tips are similar to those for other viral diseases transmitted by mosquitoes, such as dengue or West Nile :

- ❏ Use insect repellent containing DEET, Picaridin, oil of lemon eucalyptus, or IR3535 on exposed skin. Always follow the directions on the package.
- ❏ Wear long sleeves and pants (ideally treat clothes with permethrin or another repellent).
- ❏ Have secure screens on windows and doors to keep mosquitoes out.
- ❏ Get rid of mosquito sources in your yard by emptying standing water from flower pots, buckets and barrels. Change the water in pet dishes and replace the water in bird baths weekly. Drill holes in tire swings so water drains out. Keep children's wading pools empty and on their sides when they aren't being used.
- ❏ Additionally, a person with chikungunya fever should limit their exposure to mosquito bites to avoid further spreading the infection. The person should use repellents when outdoors exposed to mosquito bites or stay indoors in areas with screens or under a mosquito net.

Reference :

1. WHO

2. CDC

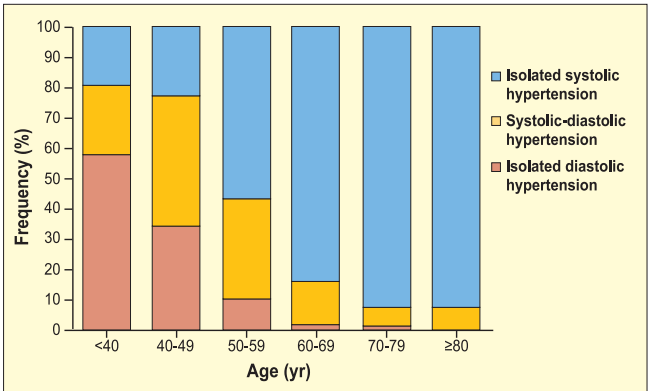
Isolated Systolic Hypertension

Hypertension is the most common cardiovascular disorder, affecting about 20% of the adult population. It is the most important modifiable risk factor for coronary heart disease, stroke, congestive heart failure, end-stage renal disease and peripheral vascular disease. Hypertension may be defined as persistent or sustained elevation of blood pressure equal or more than 140/90 mm Hg, which is average of two or more properly measured, seated BP readings for two or more office visits. According to JNC 7, classification of Blood Pressure (BP) for adults (in mm Hg):

- Normal : Systolic BP (SBP) <120 and Diastolic BP (DBP) <80
- Pre-hypertension : SBP 120-139 or DBP 80-89
- Stage 1 hypertension : SBP 140-159 or DBP 90-99
- Stage 2 hypertension : SBP 160 or DBP 100

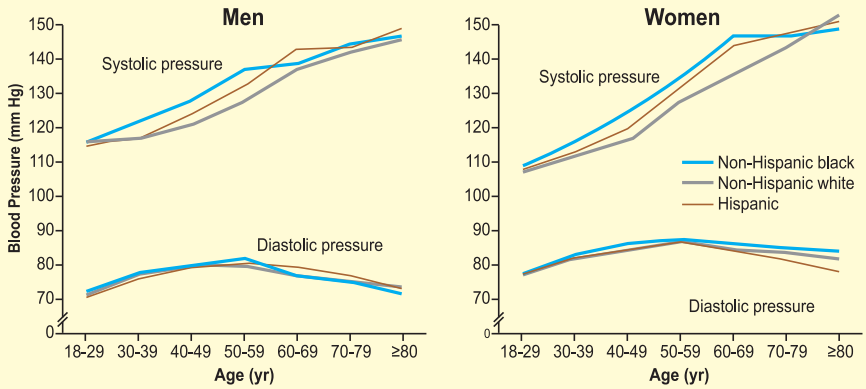
The emerging issue in the field of hypertension relates to Isolated Systolic Hypertension (ISH), a condition when systolic blood pressure (SBP) is high, but diastolic blood pressure (DBP) is normal (or even low). As per modern definitions, expressed in the JNC 7 and 1999 WHO/ISH Guidelines ISH is now defined as BP >140/<90mmHg.

These criteria are more 'stringent' than the older definition of ISH at >160/<90 mmHg. Major studies revels that isolated systolic hypertension is the most common form of hypertension in adults over the age of 60 years. This segment of the population is expanding so rapidly the ISH will soon be the most prevalent form of hypertension. In America, about 65 percent of people with hypertension over the age of 60 have isolated systolic hypertension. Despite this, it is the least treated form of hypertension. According to the Journal of Human Hypertension, less than 10 percent of individuals with isolated systolic hypertension take medication for their condition.



Frequency of Untreated Hypertension According to Subtype and Age.

Over the last couple of years, a paradigm shift has occurred, away from the prior concern over an elevation of diastolic pressure to current awareness that an elevation of systolic pressure. DBP was assumed to be the most relevant haemodynamic parameter as a predictor of prognosis in hypertensive patients. Accordingly, most clinical studies particularly addressed DBP and DBP values were put forward as goals for treatment. Since then a radical change in thinking, based upon epidemiological studies has led to the recognition of elevated systolic blood pressure as a risk factor at least as important as high DBP. Certain studies would even indicate that SBP is a more relevant predictor of prognosis than DBP, in particular with respect to the risk of stroke. This condition is found particularly in elderly hypertensives, since SBP is known to rise with advancing age, whereas DBP usually levels off and then tends to decrease in the elderly. Consequently, pulse pressure will increase in such patients. It appears that elevated pulse pressure is an even better predictor of cerebro and cardiovascular events in elderly hypertensives than a high SBP as such.



Mean Blood Pressure According to Age and Race or Ethnic Group in U.S. Adults

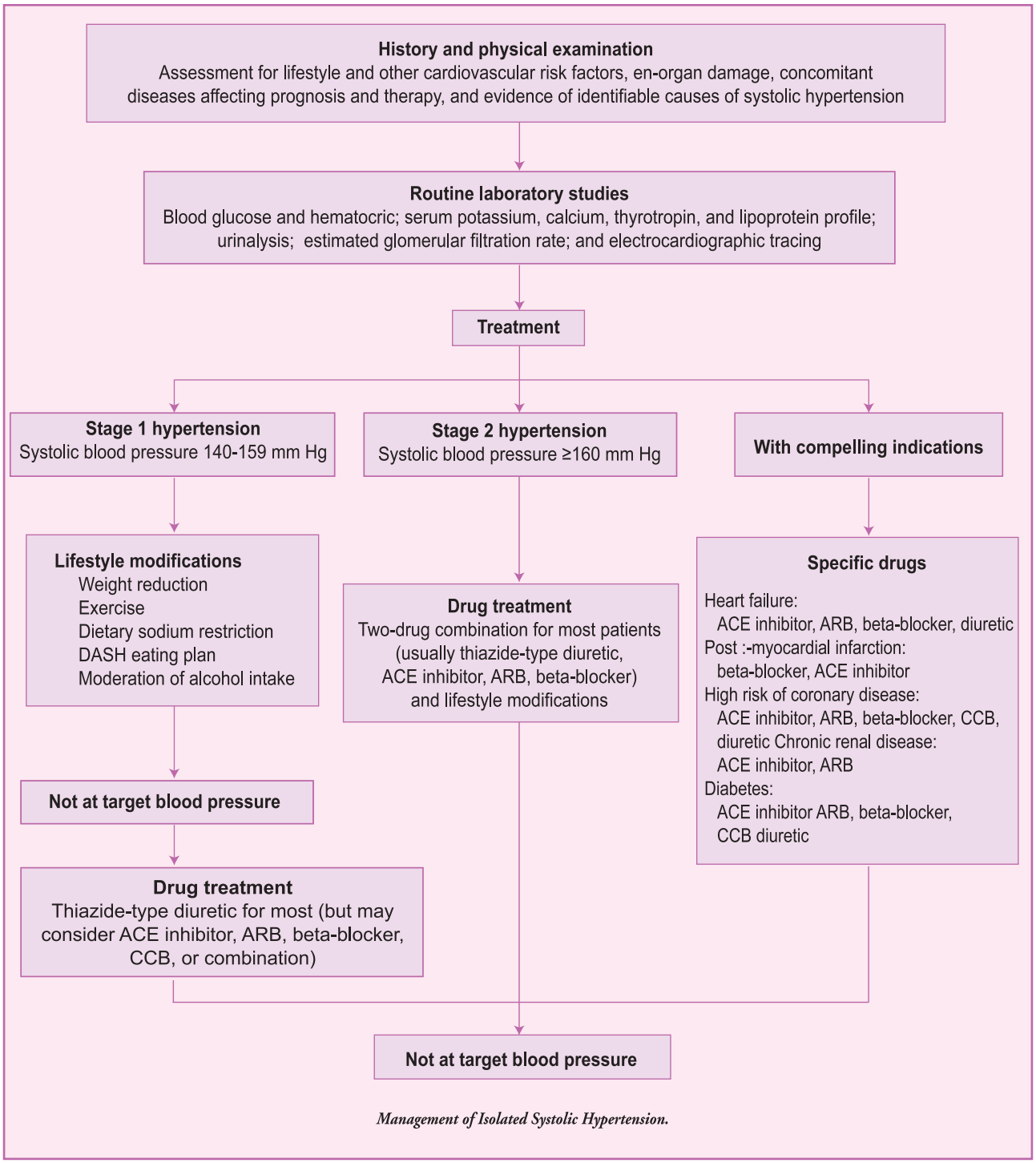
Pathophysiology

Isolated systolic hypertension may occur in conditions associated with elevated cardiac output such as anemia, hyperthyroidism, aortic insufficiency, arteriovenous fistula and Paget's disease of bone. However, the development of ISH with increasing age is explained by a deterioration of arterial compliance in particular that of the large conduit arteries.

Such increasing arterial stiffness is caused by structural and functional changes in the vascular wall, affecting collagen, extracellular protein matrix and elastin. The proliferation of connective tissue results in intimal thickening and fibrosis. The increasing vascular stiffness causes a reduction in arterial compliance and the decrease of the 'Windkessel function' of the large arteries. Stiffened conduit arteries cause an increase in the rate of return of reflected arterial pressure waves from the periphery, thereby raising the peak systolic pressure. The blood-pressure elevation itself can promote further arterial stiffening and impair endothelium-dependent vasodilatation.

Symptoms and risks

As with most cases of high blood pressure, people with isolated systolic hypertension do not usually experience any symptoms. However headache, vision changes, palpitation, increased nighttime urination may observe. Even without noticeable symptoms, isolated systolic hypertension still carries the same risks as other forms of high blood pressure.



Management of Isolated Systolic Hypertension.

Several studies, including the Framingham study, documented the risk of high SBP in particular with respect to stroke, heart attack, congestive heart failure, kidney damage, dementia, blindness and a variety of other health problems.

Patient evaluation

An assessment for the presence of other cardiovascular risk factors, end-organ damage, concomitant diseases affecting prognosis and treatment, identifiable causes of hypertension (e.g. hyperthyroidism) and potentially contributing lifestyle factors (diet and exercise) should include for initial evaluation of the patient with systolic hypertension. Physical examination should include assessment of optic fundi, thyroid, heart, lungs, kidneys, peripheral pulses and the neurologic system, with attention to signs of aortic insufficiency, hyperthyroidism, Paget's disease of bone.

Routine laboratory and electrocardiographic studies should be performed to evaluate cardiovascular risk. Laboratory tests should include urinalysis, measures of blood glucose and hematocrit, serum potassium level, estimated glomerular filtration rate and lipoprotein profile.

Management

The therapeutic approach and goals for isolated systolic hypertension are similar to those recommended for most other types of hypertension. The recommended target level of blood pressure is below 140/90 mm Hg, except in patients with diabetes or chronic renal disease, for whom a lower goal (130/80 mm Hg or lower) is advised.

The lifestyle modifications include weight reduction, restriction of dietary sodium, adoption of the DASH (Dietary Approaches to Stop Hypertension) eating plan (a diet rich in fruits, vegetables, and low-fat dairy products and low in saturated and total fat), increased physical activity and moderation of alcohol intake (no more than the equivalent of two drinks per day for men and one for women). These interventions not only reduce blood pressure but also favorably affect other risk factors for cardiovascular disease, such as diabetes, dyslipidemia, obesity etc.

Drug Treatment

Five major classes of antihypertensive drugs are most useful: diuretics, β-adrenergic blockers, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and calcium channel blockers (CCB). Each has been shown in clinical trials to reduce cardiovascular events. When used in recommended dosages, their mean effects on blood pressure are almost similar, although individual patients may have different responses to each drug. In approximately two thirds of patients with hypertension, two or more drugs may be required to achieve target blood-pressure levels.

In the Systolic Hypertension in the Elderly Program (SHEP), treatment with the diuretic agent (low dose chlorthalidone) showed impressive reductions in the incidence of stroke (-36%), coronary heart disease (-27%), and congestive heart failure (-55%), as compared with placebo.

The Joint National Committee guidelines, which have been endorsed by several professional organizations, including the American Medical Association, the American Heart Association and the American Society of Hypertension, recommend thiazide-type diuretics as initial drug therapy for most patients with isolated systolic hypertension unless there are specific contraindications for their use. The addition of a drug from another class may be required if the target blood pressure is not achieved.

On the other hand the joint guidelines of the European Society for Hypertension and the European Society of Cardiology do not give preference to diuretics and recommend any of the five major classes of antihypertensive drugs for first-line therapy. Despite some differences in recommendations, all of these guidelines emphasize that the major benefits of therapy are related to lowering blood pressure and controlling hypertension.

Conclusion

Indeed, ISH is the most common type of hypertension in the elderly and the major determinants of cardiovascular risk. The dangers of high systolic pressure are well known and unequivocal evidence shows that the treatment of ISH provides significant protection against cardiovascular mortality and morbidity. The need for effective antihypertensive therapy for the many millions of elderly patients with ISH has been reconfirmed by many authors.

There are ample of evidences that proper control of BP with appropriate therapy will prolong life a bit and more importantly, it will reduce the strokes, heart attacks and episodes of heart failure that are so burdensome to the elderly. In one of the trials of ISH treatment, the onset of dementia was also reduced, holding promise for even more benefit from such therapy.

Once established, ISH should be treated gently by bringing the systolic blood pressure to near 140 mm Hg while ensuring that the diastolic pressure is not lowered much below 70 mm Hg. The high systolic pressure must be lowered but caution is needed not to lower the already low diastolic pressure much further. In the future, drugs other than those currently recommended may have a more selective effect, lowering the elevated systolic levels but not reducing the already low diastolic levels. Special attention must obviously be paid with appropriate caution to the expanding number of vulnerable patients with ISH.

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Rotavirus Diarrhea

Diarrhea is the passage of three or more loose or liquid stools per day or more frequently than is normal for the individual. It is usually a symptom of gastrointestinal infection caused by a variety of bacterial, viral and parasitic organisms.

The specific germs that cause diarrhea can vary among geographic regions depending on their level of sanitation, economic development and hygiene. For example, developing countries with poor sanitation or where human waste is used as fertilizer often have outbreaks of diarrhea when intestinal bacteria or parasites contaminate crops or drinking water.

In developed countries, including the United States, diarrhea outbreaks are more often linked to contaminated water supplies, person-to-person contact in places such as child-care centers or "food poisoning".

In general, infections that cause diarrhea are highly contagious. Most cases can be spread to others for as long as someone has diarrhea, and some infections can be contagious even longer.

Diarrheal infections can be spread through dirty hands, contaminated food or water, some pets, direct contact with fecal matter (i.e. from dirty diapers or the toilet)

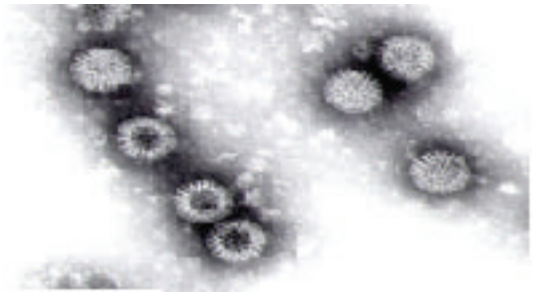
Anything that the infectious germs come in contact with can become contaminated. This includes toys, changing tables, surfaces in restrooms, even the hands of someone preparing food. Kids can become infected by touching a contaminated surface, such as a toilet or toy and then putting their fingers in their mouths.

A common cause of diarrhea is viral gastroenteritis (often called the "stomach flu," it also can cause nausea and vomiting). Many different viruses can cause viral gastroenteritis which can pass through a household, school or day-care center quickly because it is highly infectious. Although the symptoms usually last just a few days affected kids (especially infants) who are unable to get adequate fluid intake can become dehydrated.

It had taken a long time before particular viruses were identified as agents in gastrointestinal diseases. The search for viruses causing diarrheal disease was unsuccessful initially because the viruses involved failed to grow in vitro. However by the early 1970s close to 100 serotypes from at least 6 different viral families had been recovered from stools by culture. However there is little evidence that they are involved in the causation of GI disease; Viruses could be recovered from the faeces of apparently healthy persons and an association between cultivable viruses and diarrhea was rare. However it cannot be ruled out of hand that under the right circumstances, these cultivable viruses can show greater virulence in the gut and cause GI disease.

With the use of electron microscopic techniques a new group of viruses which were seen in faecal extracts but cannot be grown routinely were discovered. Electron microscopic techniques were first applied to the faecal extracts of a school outbreak in Norwalk, Ohio. Acute and convalescent serum from cases were used in an immune electron microscopic technique. 3 years passed before the discovery of the next virus associated with diarrheal disease the rotavirus. Rotaviruses and adenoviruses are regularly involved in endemic diarrhea throughout the world, whereas epidemic diarrhea is associated with small round viruses or small round structured viruses. Animal experiments have played an important role in the investigation of human disease. Diarrhea may be induced in newborn animals by challenging them with viruses extracted from human faeces. Furthermore, naturally occurring diarrheal diseases are seen in animals which are caused by viruses related to those seen in human disease.

Here, we are discussing about the diarrhea caused by rotavirus.



Electron micrograph of Rotaviruses

Rotavirus is the most common cause of severe diarrhea among infants and young children and is one of several viruses that cause infections often called stomach flu, despite being not related to influenza. It is a genus of double-stranded RNA virus in the family *Reoviridae*. By the age of five, nearly every child in the world has been infected with rotavirus at least once. However, with each infection, immunity develops and subsequent infections are less severe; adults are rarely affected. The virus is transmitted by the faecal-oral route. It infects and damages the cells that line the small intestine and causes gastroenteritis.

Rotavirus is usually an easily managed disease of childhood. Public health campaigns to combat rotavirus, focus on providing oral rehydration therapy for infected children and vaccination to prevent the disease.

Epidemiology

Rotavirus A, which accounts for more than 90% of rotavirus gastroenteritis in humans, is endemic worldwide. Each year rotavirus causes millions of cases of diarrhea in developing countries, almost 2 million resulting in hospitalization and an estimated 453,000 resulting in the death of a child younger than five. In the United States alone-before initiation of the rotavirus vaccination program-over 2.7 million cases of rotavirus gastroenteritis occurred annually, 60,000 children were hospitalized and around 37 died from the results of the infection. The major role of rotavirus in causing diarrhea is not widely recognized within the public health community, particularly in developing countries. Almost every child has been infected with rotavirus by age five.

It is the leading single cause of severe diarrhea among infants and children, being responsible for about 20% of cases and accounts for 50% of the cases requiring hospitalization. Rotavirus causes 37% of deaths attributable to diarrhea and 5% of all deaths in children younger than five. Boys are twice as likely as girls to be admitted to hospital. Rotavirus infections occur primarily during cool, dry seasons. The number attributable to food contamination is unknown.

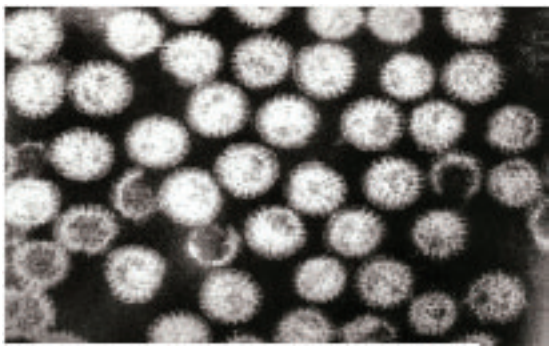
Outbreaks of rotavirus A diarrhea are common among hospitalized infants, young children attending day care centre and elderly people in nursing homes. An outbreak caused by contaminated municipal water occurred in Colorado in 1981. During 2005, the largest recorded epidemic of diarrhea occurred in Nicaragua. This unusually large and severe outbreak was associated with mutations in the rotavirus A genome, possibly helping the virus escape the prevalent immunity in the population. A similar large outbreak occurred in Brazil in 1977.

Rotavirus B, also called adult diarrhea rotavirus or ADRV, has caused major epidemics of severe diarrhea affecting thousands of people of all ages in China. These epidemics occurred as a result of sewage contamination of drinking water. Rotavirus B infections also occurred in India in 1998; the causative strain was named CAL. Unlike ADRV, the CAL strain is endemic. To date, epidemics caused by rotavirus B have been confined to mainland China and surveys indicate a lack of immunity to this species in the United States.

Rotavirus C has been associated with rare and sporadic cases of diarrhea in children in many countries and outbreaks have occurred in Japan and England.

Types of rotavirus

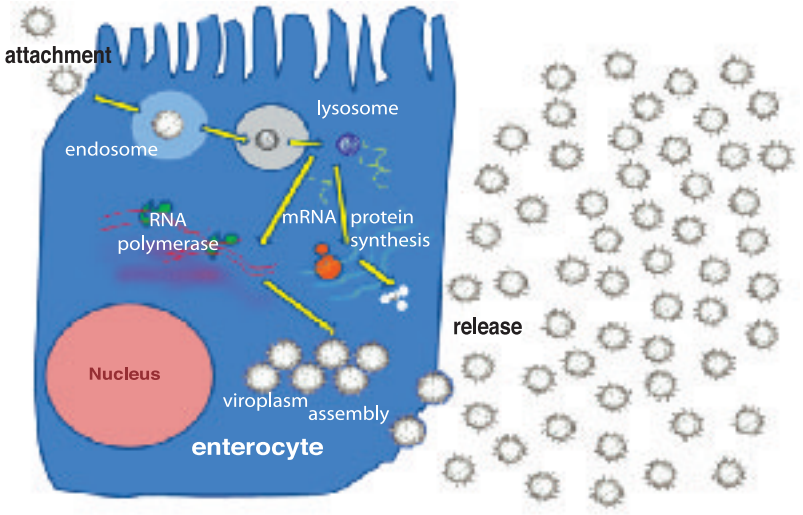
There are five species of rotavirus, referred to as A, B, C, D and E. Humans are primarily infected by species A, B and C, most commonly by species A causes more than 90% of infections in human. All five species cause disease in other animals. Within rotavirus A there are different strains, called serotypes. As with influenza virus, a dual classification system is used based on two proteins on the surface of the virus. The glycoprotein VP7 defines the G serotypes and the protease-sensitive protein VP4 defines P serotypes. Because the two genes that determine G-types and P-types can be passed on separately to progeny viruses, different combinations are found.



Rotavirus A from the faeces of an infected child

Transmission

Rotavirus is transmitted by the faecal-oral route, via contact with contaminated hands, surfaces and objects and possibly by the respiratory route. The faeces of an infected person can contain more than 10 trillion infectious particles per gram; fewer than 100 of these are required to transmit infection to another person.



A simplified drawing of the rotavirus replication cycle

Replication

Rotaviruses replicate mainly in the gut and infect enterocytes of the villi of the small intestine, leading to structural and functional changes of the epithelium. The triple protein coats make them resistant to the acidic pH of the stomach and the digestive enzymes in the gut.

The virus enter cells by receptor mediated endocytosis and form a vesicle known as an endosome. Proteins in the third layer (VP7 and the VP4 spike) disrupt the membrane of the endosome, creating a difference in the calcium concentration. This causes the breakdown of VP7 trimers into single protein subunits, leaving the VP2 and VP6 protein coats around the viral dsRNA, forming a double-layered particle (DLP).

The eleven dsRNA strands remain within the protection of the two protein shells and the viral RNA-dependent RNA polymerase creates mRNA transcripts of the double-stranded viral genome. By remaining in the core, the viral RNA evades innate host immune responses called RNA interference that are triggered by the presence of double-stranded RNA.

During the infection, rotavirus produces mRNA for both protein biosynthesis and gene replication. Most of the rotavirus proteins accumulate in viroplasm, where the RNA is replicated and the DLPs are assembled. Viroplasm is formed around the cell nucleus as early as two hours after virus infection and consists of viral factories thought to be made by two viral nonstructural proteins: NSP5 and NSP2. Inhibition of NSP5 by RNA interference results in a sharp decrease in rotavirus replication. The DLPs migrate to the endoplasmic reticulum where they obtain their third, outer layer (formed by VP7 and VP4). The progeny viruses are released from the cell by lysis.

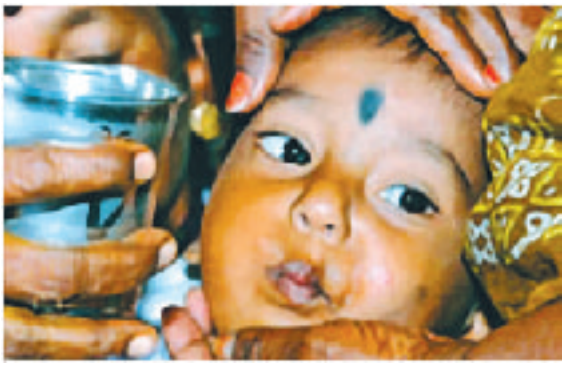
Disease mechanisms

The diarrhea is caused by multiple activities of the virus. Malabsorption occurs because of the destruction of gut cells called enterocytes. The toxic rotavirus protein NSP4 induces age- and calcium ion-dependent chloride secretion, disrupts SGLT1 transporter-mediated reabsorption of water, apparently reduces activity of brush-border membrane disaccharidases, and possibly activates the calcium ion-dependent secretory reflexes of the enteric nervous system. Healthy enterocytes secrete lactase into the small intestine; milk intolerance due to lactase deficiency is a symptom of rotavirus infection, which can persist for weeks. A recurrence of mild diarrhea often follows the reintroduction of milk into the child's diet, due to bacterial fermentation of the disaccharide lactose in the gut.

Signs and symptoms

Rotavirus gastroenteritis is a mild to severe disease characterized by vomiting, watery diarrhea, and low-grade fever. Once a child is infected by the virus, there is an incubation period of about two days before symptoms appear. Symptoms often start with vomiting followed by four to eight days of profuse diarrhea. Dehydration is more common in rotavirus infection than in most of those caused by bacterial pathogens, and is the most common cause of death related to rotavirus infection.

Rotavirus A infections can occur throughout life: the first usually produces symptoms, but subsequent infections are typically mild or asymptomatic, as the immune system provides some protection. Consequently, symptomatic infection rates are highest in children under two years of age and decrease progressively towards 45 years of age.



Maintenance of hydration

Infection in newborn children, although common, is often associated with mild or asymptomatic disease; the most severe symptoms tend to occur in children six months to two years of age, the elderly, and those with compromised or absent immune system functions.

Due to immunity acquired in childhood, most adults are not susceptible to rotavirus; gastroenteritis in adults usually has a cause other than rotavirus, but asymptomatic infections in adults may maintain the transmission of infection in the community.

Diagnosis and detection

Diagnosis of infection with rotavirus normally follows diagnosis of gastroenteritis as the cause of severe diarrhoea. Most children admitted to hospital with gastroenteritis are tested for rotavirus A. Specific diagnosis of infection with rotavirus A is made by finding the virus in the child's stool by enzyme immunoassay. There are several licensed test kits on the market which are sensitive, specific and detect all serotypes of rotavirus A.

Other methods, such as electron microscopy and PCR, are used in research laboratories. Reverse transcription-polymerase chain reaction (RT-PCR) can detect and identify all species and serotypes of human rotavirus.

Treatment and prognosis

Treatment of acute rotavirus infection is nonspecific and involves management of symptoms and most importantly, maintenance of hydration. If untreated, children can die from the resulting of severe dehydration. Depending on the severity of diarrhea, treatment consists of oral rehydration, during which the child is given extra water to drink that contains small amounts of salt and sugar. Some infections are serious enough to warrant hospitalization where fluids are given by intravenous drip or nasogastric tube, and the child's electrolytes and blood sugar are monitored. Rotavirus infections rarely cause other complications and for a well managed child the prognosis is excellent.

Rotavirus vaccination

Prevention

Rotavirus vaccine has the potential to decrease rates of diarrhea. There are currently two licensed vaccines against rotavirus. These vaccines against Rotavirus A infection are safe and effective in children. Both are taken orally and contain attenuated live virus.

Use of the vaccine should be part of a comprehensive diarrheal disease control strategy including, among other interventions, improvements of hygiene and sanitation, zinc supplementation, community-based administration of oral rehydration solution and overall improved case management.

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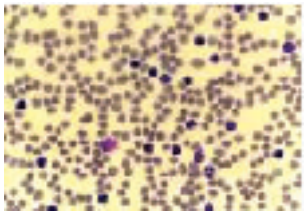
Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (chronic lymphoid leukemia, CLL) is a monoclonal disorder characterized by a progressive accumulation of functionally incompetent lymphocytes. It is the most common form of leukemia found in adults in Western countries.



Histologic sample

Peripheral smear from a patient with chronic lymphocytic leukemia, small lymphocytic variety. Onset is insidious and it is not unusual for CLL to be discovered incidentally after a blood cell count is performed for another reason. Enlarged lymph nodes are the most common presenting symptom but patients may present with a wide range of symptoms and signs.

Chemotherapy is not needed in CLL until patients become symptomatic or display evidence of rapid progression of disease. A variety of chemotherapy regimens are used in CLL. These may include nucleoside analogues, alkylating agents and biologics, often in combination. Allogeneic stem cell transplantation is the only known curative therapy.

Pathophysiology

The cells of origin in most patients with CLL are clonal B cells arrested in the B-cell differentiation pathway, intermediate between pre-B cells and mature B cells. Morphologically, in the peripheral blood, these cells resemble mature lymphocytes.

CLL B-lymphocytes typically show B-cell surface antigens, as demonstrated by CD19, $CD20^{dim}$, CD21 and CD23 monoclonal antibodies. In addition, they express CD5, which is more typically found on T cells. Because normal $CD5^{+}$ B cells are present in the mantle zone of lymphoid follicles, B-cell CLL is most likely a malignancy of a mantle zone-based subpopulation of anergic self-reactive cells devoted to the production of polyreactive natural autoantibodies.

CLL B-lymphocytes express extremely low levels of surface membrane immunoglobulin, most often immunoglobulin M (IgM) or IgM/IgD and IgD. Additionally, they also express extremely low levels of a single immunoglobulin light chain (kappa or lambda).

An abnormal karyotype is observed in the majority of patients with CLL. The most common abnormality is deletion of 13q, which occurs in more than 50% of patients. Individuals showing 13q14 abnormalities have a relatively benign disease that usually manifests as stable or slowly progressive isolated lymphocytosis.

The presence of trisomy 12, which is observed in 15% of CLL patients, is associated with atypical morphology and progressive disease. Deletion in the short arm of chromosome 17 has been associated with rapid progression, short remission and decreased overall survival. 17p13 deletions are associated with loss of function of the tumor suppressor gene *p53*. Deletions of bands 11q22-q23, observed in 19% of patients, are associated with extensive lymph node involvement, aggressive disease and shorter survival.

More sensitive techniques have demonstrated abnormalities of chromosome 12. 40% to 50% of patients demonstrate no chromosomal abnormalities on conventional cytogenetic studies. However, 80% of patients will have abnormalities detectable by fluorescence in situ hybridization (FISH). Approximately 2-5% of patients with CLL exhibit a T-cell phenotype.

Studies have demonstrated that the proto-oncogene *bcl2* is overexpressed in B-cell CLL. The proto-oncogene *bcl2* is a known suppressor of apoptosis (programmed cell death), resulting in a long life for the involved cells. Despite the frequent overexpression of bcl-2 protein, genetic translocations that are known to result in the overexpression of *bcl2*, such as t(14;18), are not found in patients with CLL.

Studies have shown that this upregulation in *bcl2* is related to deletions of band 13q14. Two genes, named *miRNA15a* and *miRNA16-1*, are located at 13q14 and have been shown to encode not for proteins, but rather for a regulatory RNA called microRNA (miRNA). These miRNA genes belong to a family of highly conserved noncoding genes throughout the genome whose transcripts inhibit gene expression by causing degradation of mRNA or by blocking transcription of mRNA.

Deletions of *miRNA15a* and *miRNA16-1* lead to overexpression of *bcl2* through loss of downregulating *miRNAs*. Genetic analyses have demonstrated deletion or downregulation of these miRNA genes in 70% of CLL cases.

Investigations have also identified a number of high-risk genetic features and markers, including the following:

- Germline immunoglobulin variable heavy chain (IgV_H)
- IgV_H*V3-21* gene usage
- Increased CD38 expression
- Increased Zap70 expression
- Elevated serum beta-2-microglobulin levels
- Increased serum thymidine kinase activity
- Short lymphocyte doubling time (< 6 mo)
- Increased serum levels of soluble CD23

These features have been associated with rapid progression, short remission, resistance to treatment and shortened overall survival in patients with CLL.

Germline IgV_H has been shown to indicate a poor prognosis. Studies have shown that these patients also have earlier progression of CLL after treatment with chemotherapy.

Zeta-associated peptide of 70 kilodaltons (Zap70) is a cytoplasmic tyrosine kinase whose expression has been associated with a poor prognosis. Cells with germline IgV_H often have an increased expression of Zap70; however, studies have shown discordance rates of 10-20% between IgVH mutational status and Zap70 expression levels. Elevated levels of Zap70 are believed to decrease the threshold for signaling through bcl2, thereby facilitating the antiapoptotic effects of *bcl2*.

Etiology

As in the case of most malignancies, the exact cause of CLL is uncertain. CLL is an acquired disorder and reports of truly familial cases are exceedingly rare.

Epidemiology

United States statistics

More than 17,000 new cases of CLL are reported every year. The true incidence in the US is unknown and is likely higher, as estimates of CLL incidence come from tumor registries and many cases are not reported.

International statistics

Although the incidence of CLL in Western countries is similar to that of the United States, CLL is extremely rare in Asian countries (ie, China, Japan), where it is estimated to comprise only 10% of all leukemias. However, underreporting and incomplete registry may significantly underestimate the true incidence of CLL in these countries.

Race, sex and age-related demographics

The incidence of CLL is higher among whites than blacks. The incidence of CLL is higher in males than in females, with a male-to-female ratio of 1.7:1.

CLL is a disease that primarily affects the elderly, with the median age of presentation being 72 years. Median age is 58 years in familial cases.

Clinical Presentation

Patients with chronic lymphocytic leukemia (chronic lymphoid leukemia, CLL) present with a wide range of symptoms and signs. Onset is insidious and it is not unusual for CLL to be discovered incidentally after a blood cell count is performed for another reason; 25-50% of patients will be asymptomatic at time of presentation.

Enlarged lymph nodes are the most common presenting symptom, seen in 87% of patients symptomatic at time of diagnosis. A predisposition to repeated infections such as pneumonia, herpes simplex labialis, and herpes zoster may be noted. Early satiety and/or abdominal discomfort may be related to an enlarged spleen.

Mucocutaneous bleeding and/or petechiae may be due to thrombocytopenia. Tiredness and fatigue may be present secondary to anemia; 10% of patients with CLL will present with an autoimmune hemolytic anemia.

Richter syndrome or Richter transformation refers to the transformation of CLL into an aggressive large B-cell lymphoma and is seen in approximately 3-10% of cases. Patients will often present with symptoms of weight loss, fevers, night sweats, muscle wasting (ie, B symptoms) and increasing hepatosplenomegaly and lymphadenopathy. Treatment remains challenging and prognosis poor, with median survival in months.

Autoimmune Manifestations

Autoimmune manifestations in CLL are myriad, as follows :

- ❏ Positive DAT (Coombs test) without autoimmune hemolytic anemia (AIHA)
- ❏ AIHA
- ❏ Immune thrombocytopenia (ITP)
- ❏ Pure red cell aplasia
- ❏ Autoimmune neutropenia
- ❏ Cold agglutinin disease
- ❏ Paraneoplastic pemphigus
- ❏ Neuropathies
- ❏ Evans syndrome

Up to 25% of patients with CLL demonstrate autoimmune anemia, thrombocytopenia or both. Simultaneously, immune incompetence is present, characterized by a progressive profound hypogammaglobulinemia, predisposing patients to a number of infections, the most common being bacterial pneumonias.

Patients experiencing frequent bacterial infections associated with hypogammaglobulinemia are likely to benefit from monthly infusions of intravenous immunoglobulin (IVIG). Studies of prophylactic IVIG in patients with CLL have not demonstrated a survival benefit, but have shown a significant decrease in the occurrence of major infections and a significant reduction in clinically documented infections.

Prednisone alone, usually in a dose of 20-60 mg daily initially, with subsequent gradual dose reduction, may be useful in patients with AIHA. Rituximab, alone or as part of a combination regimen, can be very effective in eliminating the B-cell clone that induces autoimmune disorders, particularly for patients with autoimmune thrombocytopenia. IVIG can be used as a short-term measure in patients who have severe thrombocytopenias or pending surgery. Thrombopoietin receptor agonists have been used with some success as in primary ITP.

The previous notion that purine analogs are more prone to result in autoimmune cytopenias has been recently challenged by data from studies such as the UK CLL4 trial.

Extremely high white blood cell counts (>300,000/µL) may produce a hyperviscosity syndrome with altered central nervous system function and/or respiratory insufficiency. Leukocytapheresis and urgent therapy with prednisone and chemotherapy may be required. Virtually all patients requiring therapy should also be given allopurinol to prevent uric acid nephropathy.

Occasionally, nonimmune manifestations due to antibodies may occur, such as renal toxicity from monoclonal gammopathy due to CLL.

Diagnostic Consideration

Mantle cell lymphoma can have a clinical presentation very similar to chronic lymphocytic leukemia (chronic lymphoid leukemia, CLL) but more aggressive.

Several features aid in the distinction of mantle cell lymphoma from CLL. Mantle cell lymphoma expresses CD5 and CD19 but not CD23 antigen, which is expressed in CLL. Mantle cell lymphoma typically expresses FMC-7. Importantly, expression of CD20 is bright in mantle cell lymphoma, whereas it is dim in CLL.

Anemia secondary to bone marrow involvement with CLL, splenic sequestration of red blood cells and autoimmune hemolytic anemia associated with a positive Coombs test are included in the differential diagnosis of a patient with anemia who has CLL.

Another problem to be considered is splenic lymphoma with villous lymphocytes.

Differential diagnosis are :

- Acute Lymphoblastic Leukemia
- Hairy Cell Leukemia
- Lymphoma, Diffuse Large Cell
- Lymphoma, Follicular
- Lymphoma, Lymphoblastic
- Lymphoma, Mantle Cell
- Lymphoma, Non-Hodgkin
- Small Lymphocytic Lymphoma
- T-Prolymphocytic leukemia (Former T-CLL)

Approach Considarations

In patients with chronic lymphocytic leukemia (chronic lymphoid leukemia, CLL), the complete blood count (CBC) with differential shows absolute lymphocytosis, with more than 5000 B-lymphocytes/µL. Lymphocytosis must persist for longer than 3 months. Clonality must be confirmed by flow cytometry. The presence of a cytopenia caused by clonal bone marrow involvement establishes the diagnosis of CLL regardless of the peripheral B-lymphocyte count.

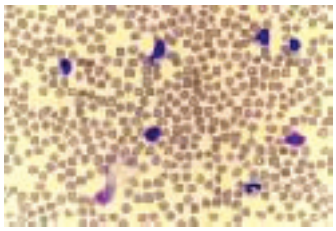
Patients with fewer than 5000 B-lymphocytes/µL with lymphadenopathy and without cytopenias more likely have small lymphocytic lymphoma (SLL), although this diagnosis should be confirmed by lymph node biopsy.

Patients with a clonal B-cell population less than 5000/µL without lymphadenopathy or organomegaly, cytopenia or other disease-related symptoms have monoclonal B-lymphocytosis (MBL). MBL will progress to CLL at a rate of 1-2% per year.

Microscopic examination of the peripheral blood smear is indicated to confirm lymphocytosis. It usually shows the presence of smudge cells, depicted in the image below, which are artifacts from lymphocytes damaged during the slide preparation.

Peripheral smear from a patient with chronic lymphocytic leukemia, large lymphocytic variety. Smudge cells are also observed; smudge cells are the artifacts produced by the lymphocytes damaged during the slide preparation.

Large atypical cells, cleaved cells and prolymphocytes are also often seen on the peripheral smear and may account for up to 55% of peripheral lymphocytes. If this percentage is exceeded, prolymphocytic leukemia (B-cell PLL) is a more likely diagnosis.



Peripheral blood smear

Peripheral blood flow cytometry is the most valuable test to confirm a diagnosis of chronic lymphocytic leukemia (chronic lymphoid leukemia, CLL). It confirms the presence of circulating clonal B-lymphocytes expressing CD5, CD19, CD20(dim), CD 23 and an absence of FMC-7 staining.

Consider obtaining serum quantitative immunoglobulin levels in patients developing repeated infections, because monthly intravenous immunoglobulin administration in patients with low levels of immunoglobulin G (IgG) (< 500 mg) may be beneficial in reducing the frequency of infectious episodes.

The differential diagnosis of CLL includes several other entities, such as hairy cell leukemia, which is moderately positive for surface membrane immunoglobulins of multiple heavy-chain classes and is typically negative for CD5 and CD21.

Prolymphocytic leukemia has a typical phenotype that is positive for CD19, CD20 and surface membrane immunoglobulin; one half will be negative for CD5. Large granular lymphocytic leukemia has a natural killer (NK) cell phenotype (CD2, CD16 and CD56) or a T-cell immunotype (CD2, CD3 and CD8). The pattern of positivity for CD19, CD20 and the T-cell antigen CD5 is shared only by mantle cell lymphoma; these cells generally do not express CD23.

Splenic lymphoma with villous lymphocytes is strongly positive for surface immunoglobulin and positive for FMC-7, CD22, CD79b and DBA-44. Follicular lymphoma is also strongly positive for surface immunoglobulin, positive for FMC-7, CD22, CD10, CD79b and weak CD23.

Bone marrow aspiration and biopsy with flow cytometry is not required in all cases of CLL. However, it may be necessary in selected cases to establish the diagnosis and to assess other complicating features such as anemia and thrombocytopenia.

Liver/spleen ultrasonographic studies may demonstrate splenomegaly in patients with CLL. CT scanning of the chest, abdomen or pelvis is generally not required for staging purposes in CLL. However, be careful to not miss lesions such as obstructive uropathy or airway obstruction that are caused by lymph node compression on organs or internal structures.

Serum free light chain (FLC) assays remain a research tool. Monoclonal and polyclonal abnormalities have been detected in half the patients and appear to be associated with poor time to first treatment.

Chromosomal Testing

Although not necessary for the diagnosis or staging of CLL, additional molecular testing now exists that may help predict prognosis or clinical course.[14, 15, 16, 17] At present, these tests are not recommended for routine use, although this may change with further research.

Chromosomal evaluation using fluorescence in situ hybridization (FISH) can identify certain chromosomal abnormalities of CLL with prognostic significance. Patients with a deletion in the short arm of chromosome 17 [del(17p)] tend to have a worse prognosis, as well as resistance to therapy with alkylating agents and purine analogues. Patients with deletions in the long arm of chromosome 11 [del(11q)] also have a worse prognosis and bulky lymphadenopathy at presentation.

The poor prognosis seen with del(17p) and del (11q) are independent of the patient's stage at presentation. Patients with these abnormalities may benefit from treatment with the monoclonal antibody alemtuzumab.

IgVH status has shown potential as a prognostic marker for CLL as well. ZAP-70 and CD38 expression tend to correlate with unmutated IgVH and a better prognosis; however, these associations are not absolute. Further clinical information is necessary to determine the role that testing for these markers should play in the management of chronic lymphocytic leukemia (chronic lymphoid leukemia, CLL).

None of the poor prognostic markers has been validated as an indication to initiate treatment in asymptomatic patients.

MicroRNA analysis remains a research tool. miR-181b levels appear to decrease in blood samples of patients whose disease is progressive.

Bone marrow aspiration and biopsy:

Bone marrow aspiration and biopsy with flow cytometry is not required in all cases of CLL but it may be necessary in selected cases to establish the diagnosis and to assess other complicating features such as anemia and thrombocytopenia. For example, bone marrow examination may be necessary to distinguish between thrombocytopenia of peripheral destruction (in the spleen) and that due to marrow infiltration.

Consider a lymph node biopsy if lymph node(s) begin to enlarge rapidly in a patient with known CLL, to assess the possibility of transformation to a high-grade lymphoma. When such transformation is accompanied by fever, weight loss and pain, it is termed Richter syndrome.

Staging

Two staging systems are in common use for CLL: the modified Rai staging in the United States and the Binet staging in Europe. Neither is completely satisfactory and both have often been modified. Because of its historical precedent and wide use, the Rai-Sawitsky system is described first, followed by the Binet.

These CLL staging systems have been unable to provide information regarding disease progression due to its heterogeneity.

Rai-Sawitsky staging system

The original 5-stage Rai-Sawitsky staging system was revised in 1987 to a simpler 3-stage system. The revised Rai staging system divides patients into low-, intermediate- and high-risk groups, as follows:

- Low risk (formerly stage 0) - Lymphocytosis in the blood and marrow only (25% of presenting population)
- Intermediate risk (formerly stages I and II) - Lymphocytosis with enlarged nodes in any site or splenomegaly or hepatomegaly (50% of presentation)
- High risk (formerly stages III and IV) - Lymphocytosis with disease-related anemia (hemoglobin < 11 g/dL) or thrombocytopenia (platelets < 100 x 10^9/L) (25% of all patients)

Binet staging system

The Binet stages are as follows:

- Stage A - Hemoglobin greater than or equal to 10 g/dL, platelets greater than or equal to 100 x 10^9/L and fewer than 3 lymph node areas involved.
- Stage B - Hemoglobin and platelet levels as in stage A and 3 or more lymph node areas involved
- Stage C - Hemoglobin less than 10 g/dL or platelets less than 100 x10^9/L or both

After successful treatment of immune cytopenias, CLL may be down-staged,

Treatment

Approach Considerations

Patients with chronic lymphocytic leukemia (chronic lymphoid leukemia, CLL) do not need to be treated with chemotherapy until they become symptomatic or display evidence of rapid progression of disease, as characterized by the following:

- Weight loss of more than 10% over 6 months
- Extreme fatigue
- Fever related to leukemia for longer than 2 weeks
- Night sweats for longer than 1 month
- Progressive marrow failure (anemia or thrombocytopenia)
- Autoimmune anemia or thrombocytopenia not responding to glucocorticoids
- Progressive or symptomatic splenomegaly
- Massive or symptomatic lymphadenopathy
- Progressive lymphocytosis, as defined by an increase of > 50% in 2 months or a doubling time of less than 6 months

Patients with low-risk (Binet A) disease whose CLL is stable require only periodic follow-up. In multiple studies and a meta-analysis, early initiation of chemotherapy has failed to show benefit in CLL; indeed, it may increase mortality. As such, early therapy should be considered only in the setting of a clinical trial.

Attempts to consolidate major clinical, chromosomal and serum markers into a single nomogram/model are underway but are as of yet far from widespread acceptance.

A variety of chemotherapy regimens are used in CLL. These may include nucleoside analogues, alkylating agents and biologics, often in combination. Allogeneic stem cell transplantation is the only known curative therapy. The complete response (CR) is defined by absence of lymphocytosis, lymphadenopathy and organomegaly without significant cytopenias.

Patients with CLL are prone to infections, both common and unusual. Pneumococcal and influenza vaccines are recommended.

Long-term monitoring

Growth factors may be used in order to decrease the length of neutropenia following chemotherapy in patients with Chronic Lymphoid Leukemia.

Chemotherapy Regimens

Nucleoside analogues constitute a class of drugs with major activity against indolent lymphoid malignancies, including CLL. Agents in this class include fludarabine, cladribine and pentostatin. Fludarabine is the most extensively studied of these nucleoside analogues and is currently the most commonly used first-line therapy in CLL.

It should be noted that many clinical trials in CLL represent a younger population, which can tolerate aggressive chemotherapy regimens to show impressive results.

While chlorambucil is a forgotten drug in the United States, likely primarily due to low cost, it is still used as first-line in elderly, fragile populations in Europe, which make up the bulk of true CLL cases. In the CLL5 study comparing fludarabine with chlorambucil (median age 70 y), while there was significantly higher response rate with fludarabine, progression-free survival was similar (19 vs 18 mo). Overall survival was not significantly affected either, although it was 46 months with fludarabine compared with 64 months for chlorambucil.

Various combination regimens have shown improved response rates in several randomized trials but also have failed to show any survival advantage. Common combination regimens include the following:

- Fludarabine, cyclophosphamide, and rituximab (FCR)
- Pentostatin, cyclophosphamide, and rituximab (PCR)
- Fludarabine, cyclophosphamide, and mitoxantrone (FCM)
- Cyclophosphamide, vincristine, and prednisone (CVP)
- Cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP)

A study by Robak et al showed that cladribine or fludarabine, in combination with cyclophosphamide, are equally effective in previously untreated progressive CLL. The authors concluded that cladribine or fludarabine and cyclophosphamide are safe first-line regimens for progressive CLL; however, both combinations have unsatisfactory activity in patients with 17p13 (TP53 gene) deletion.

A bendamustine/rituximab combination has had some renewed interest. In a German phase II study of 72 pretreated patients, overall response rate was 59% and PFS was almost 15 months.

Alemtuzumab

Alemtuzumab is a monoclonal antibody directed at CD52 that is approved for use in CLL as both a first-line agent and for salvage in patients with fludarabine-refractory disease. Alemtuzumab has been shown to be effective in treating CLL with p53 mutations [del(17p13.1)]. This is in contrast to rituximab, which is not effective in p53 mutation-bearing CLL. Although very effective in clearing the bone marrow of disease, alemtuzumab has shown only limited activity in clearing bulky lymphadenopathy.

Alemtuzumab appears to have a role in consolidation therapy for the elimination of minimal residual disease (MRD). In one study, 38% of patients treated with alemtuzumab consolidation after induction chemotherapy had molecular disease remission. Of note, 3 patients in this study developed Epstein-Barr virus-positive large B-cell lymphoma; 2 of these lymphomas resolved spontaneously and the third responded to cidofovir and immunoglobulin.

Two phase II studies from have evaluated aggressive regimens CFAR (FCR and alemtuzumab) for high-risk CLL as frontline and salvage treatment. Although the median PFS was 38 months and the median OS was not reached in the frontline study, the therapy may be of interest as a regimen to achieve CR in the 17p deletion CLL population before allogeneic stem cell transplantation in selected patients with excellent performance status.

In pretreated patients, when used as salvage and compared with FCR, the addition of alemtuzumab to FCR did not show any improvement in PFS or OS. Serious infections developed in 74% of patients at some point during or after treatment.

The German CLL Study Group prematurely closed a phase III trial involving alemtuzumab consolidation due to severe infections in the alemtuzumab arm; however, this has not been seen in other studies to date.

Antiviral prophylaxis and prophylactic antibiotics for Pneumocystis jiroveci are recommended for use in patients receiving alemtuzumab during and for 2-4 months after treatment, or until their CD4 count is >250x109 cells. Cytomegalovirus (CMV) polymerase chain reaction (PCR) is also recommended to monitor for CMV reactivation. If CMV is detected, alemtuzumab should be discontinued and appropriate treatment initiated until CMV becomes undetectable.

Investigational monoclonal antibodies

Ofatumumab is a new anti-CD20 monoclonal fully humanized antibody. It has been approved by US Food and Drug Administration (FDA) for the treatment of patients with CLL refractory to fludarabine and alemtuzumab. In a phase II trial, the response rate was 42%, with a median duration of response of 6.5 months in this heavily pretreated population. Additional studies in combination trials are being done.

Other monoclonal antibodies in development that are undergoing study in CLL include hLL1, epratuzumab, and lumiliximab.

Combination therapy with monoclonal antibodies

Relatively recent trials have investigated the combination of monoclonal antibodies with chemotherapeutic agents. Rituximab as a single agent has shown only partial responses of short duration, but it has been used extensively in combination with chemotherapy drugs (eg, fludarabine). Patients with trisomy 12q may express higher levels of CD20, thus making tumor cells more vulnerable to biologics against CD20.

Fludarabine has been shown to downregulate CD55 and CD59; these are proteins involved in complement resistance and their loss enhances the action of rituximab. Fludarabine combined with rituximab has been shown to have higher clinical remission rates than fludarabine alone in clinical trials.

The combination of fludarabine and cyclophosphamide with rituximab (FCR) has shown clinical response rates of 76% in trials. This result is better than those seen with either fludarabine or FC in salvage therapy for patients with previously treated CLL.

Robak et al found that outcome in patients with previously treated CLL was significantly better with FCR than with fludarabine and cyclophosphamide alone (FC). Their study compared 6 cycles of FCR (n = 276) with 6 cycles of FC (n = 276). After a median follow-up time of 25 months, progression-free survival was significantly higher with FCR than with FC (median, 30.6 versus 20.6 mo, respectively).

In addition, patients receiving FCR demonstrated significantly better event-free survival, response rate, complete response rate, duration of response and time to new CLL treatment or death.

A prospective, single-arm study of patients treated initially with fludarabine and rituximab reported that median overall survival was 85 months. After 5 years, 71% of patients were alive and 27% remained free of disease. Another study found that the addition of rituximab to a standard chemotherapy regimen of fludarabine and cyclophosphamide improved efficacy with little increase in toxicity. The combination of cyclophosphamide, fludarabine, alemtuzumab, and rituximab (CFAR) is currently under study in clinical trials.

A phase III study is under way in Europe that compares fludarabine with and without alemtuzumab. Alemtuzumab with rituximab appears to be well tolerated and have a high response rate; however, a short time to progression indicates that perhaps the dosing schedule needs further refinement.

Lenalidomide

Lenalidomide is an immunomodulatory drug (IMiD) currently approved for use in multiple myeloma and myelodysplastic syndrome with deletion of chromosome 5q. Studies have utilized this medication in treatment of patients with relapsed and refractory CLL. Response rates of 47-38% with complete response rates of 9% and elimination of MRD have also been reported.

Transplantation

Allogeneic stem cell transplantation is the only known curative therapy. The optimal timing of transplantation is still being investigated; however, it is known that delay of transplantation until development of refractory disease results in worse outcomes. However, remember that most patients are elderly and too fragile to consider upfront stem-cell transplantation in first clinical remission.

The effectiveness of nonmyeloablative transplantation has shown that there is a graft versus leukemia effect in CLL. Autologous transplantation after high-dose conditioning has not been shown to provide a survival advantage and is not recommended outside the setting of a clinical trial. Alemtuzumab is being investigated for use in hematopoietic stem cell transplantation (HSCT). This agent may play an important role in the elimination of MRD in patients undergoing autologous transplantation, while, at the same time, the lack of CD52 on hematopoietic stem cells prevents interference with stem cell collection.

The addition of alemtuzumab to nonmyeloablative conditioning regimens for allogeneic HSCT appears to decrease the incidence of graft versus host disease (GVHD), but it may be associated with increased rates of cytomegalovirus reactivation. A study by Michallet et al indicated that patients who had responded to first-line or second-line therapy experienced a longer duration of time until progression, death or subsequent treatment if they underwent autologous stem cell transplantation instead of observation.

Splenectomy

Refractory splenomegaly and pancytopenia is a common problem in patients with advanced CLL. Occasionally, these patients require splenectomy. Substantial improvements in hemoglobin and platelet counts are observed in up to 90% of patients undergoing splenectomy. All patients with CLL who are to undergo splenectomy should be immunized at least 1 week in advance against the pneumococcus, Haemophilus influenza and Neisseria meningitidis.

Medication

Chlorambucil and fludarabine are commonly used in the treatment of chronic lymphocytic leukemia (chronic lymphoid leukemia, CLL). Purine analogues, fludarabine in particular, are very active against CLL. Fludarabine produces remissions in a significant proportion of patients. It appears to induce apoptosis in malignant lymphocytes upon exposure.

Antineoplastic Agents

Antineoplastic agents act by inhibiting the key factors responsible for neoplastic transformation of cells.

Pentostatin

Pentostatin inhibits adenosine deaminase, resulting in deoxyadenosine and deoxyadenosine 5+-triphosphate accumulation that may inhibit DNA or RNA synthesis, causing cell death.

Chlorambucil

Chlorambucil is a nitrogen mustard derivative with bifunctional alkylating activity. It forms intrastrand crosslinks, interfering with DNA replication and RNA transcription and translation.

Fludarabine

A nucleotide analogue of vidarabine, fludarabine is converted to 2-fluoro-ara-A, which enters the cell and is phosphorylated to form active metabolite 2-fluoro-ara-ATP, which inhibits DNA synthesis.

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody against CD52, an antigen found on B-cells, T-cells and almost all CLL cells. It binds to the CD52 receptor of the lymphocytes, which slows the proliferation of leukocytes.

Rituximab

Rituximab is a humanized murine monoclonal antibody against CD20, an antigen found on B-cells. This agent binds CD20 on lymphocytes and induces apoptosis as well as initiating complement-mediated killing of bound cells. Because CLL B-cells have low levels of CD20 expression, increased doses of rituximab may be necessary.

Ofatumumab

Ofatumumab is an anti-CD20 human monoclonal antibody that inhibits B-cell activation in early stages. It is indicated for CLL refractory to fludarabine and alemtuzumab. Its effectiveness is based on objective responses; improvement in disease or symptoms or increased survival was not demonstrated.

Prognosis

The prognosis of patients with CLL varies widely at diagnosis. Some patients die rapidly, within 2-3 years of diagnosis, because of complications from CLL. Most patients live 5-10 years, with an initial course that is relatively benign but followed by a terminal, progressive and resistant phase lasting 1-2 years. During the later phase, morbidity is considerable, both from the disease and from complications of therapy.

Prognosis depends on the disease stage at diagnosis as well as the presence or absence of high-risk markers

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Glimpse of MSD Activities

Scientific Seminar of OGSB, Chittagong, January 2012

Intern Reception Program of 37th batch, SBMC&H Barisal, February 2012

Scientific Seminar on Hospital Documentation at BMC&H Dhaka, November 2011

Intern Reception Program of MMC&H Mymensingh, December 2011

SQUARE Pharmaceuticals Ltd. has been awarded National Export Trophy "Silver" for its excellent performance in pharmaceutical export in the year 2009 -2010

"Executive Director, Marketing receiving the award, given by Dun & Bradstreet Ltd. on behalf of *SQUARE* Pharmaceuticals Ltd. for its' outstanding achievement in Pharmaceutical category in the year of 2010."

SQUARE Pharmaceuticals Ltd., participated in the 7th International Pharmaceutical and Medical Exhibition "PharmMedExpo Uzbekistan" held in Tashkent.

A group of doctors from Afghanistan has visited *SQUARE* Pharmaceuticals Ltd's Dhaka Unit.

Test Yourself - 27

Correct Answers :

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

CONGRATULATIONS!

WINNERS

Dr. Md. Khurshedul Alam
Surgery Unit - 3
SSMC&MH, Dhaka

Dr. Md. Masudur Rahman
MBBS, DTCD
Khan Medical Centre
Anantobazar, Pabna

Dr. N. C. dey *MBBS*
A. Jaman Diagnostic Clinic
Sreebordi, Sherpur

Dr. Md. Abdus Salam
M. Phil (Psychiatry)
Sadar Hospital, Jhenaidah

Dr. A. I. Zoarder
MBBS, D-Card
Apollow Pharmacy
DIT Plot, Gandaria

Dr. Mozaharul Islam
Medical Officer
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Dr. S. M. Moniruzzaman
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Dr. Shanjida Sharmin
Asst. Registrar, Pead
Unit - 1, DMCH

Dr. Md. Shahidullah Kaiser
Consultant (Ortho.),
General Hospital, Tangail

Dr. Nilofar Yasmin *MBBS*
D/7/E, Railway Officers Colony,
Kamalapur, Dhaka

Test Yourself - 28

1. **All the followings are true for Chikungunya Fever except:**
   a. The disease was first described in 1955.
   b. It is spread by the bite of an Aedes aegypti.
   c. An infected person can spread the infection directly to others.
   d. Most patients fully recovers but some cases joint pain may persists.

2. **The followings are correct for Isolated Systolic Hypertension(ISH) except:**
   a. ISH is most common form of Hypertension in adult >40 years of age.
   b. ISH may occur in conditions associated with elevated cardiac output.
   c. Five major classes of antihypertensive drugs are most useful.
   d. In most cases of people with ISH do not usually experience any symptoms.

3. **All the below are true for Chikungunya Fever except:**
   a. ELISA may confirm the presence of IgM and IgG anti chikungunya antibodies.
   b. Fever and pain can be relieved by using aspirin.
   c. There is no vaccine or specific antiviral treatment currently available for this.
   d. The best way to prevent this infection is to avoid mosquito bites.

4. **All the followings are correct for Chronic Lymphocytic Leukemia(CLL) except:**
   a. CLL is characterized by a progressive accumulation of functionally incompetent lymphocytes.
   b. The onset of CLL is abrupt.
   c. Chemotherapy not needed in CLL until patient became symptomatic.
   d. The exact cause of CLL is uncertain.

5. **The followings are right for Rotavirus except:**
   a. It is the most common cause of severe diarrhea among infants and young children.
   b. The virus is transmitted by the faecal - oral route.
   c. There are six species of Rotavirus.
   d. Species A causes more than 90% of infections in human.

6. **All the followings are correct for Chronic Lymphocytic Leukemia (CLL) except:**
   a. 25-50% of patients will be asymptomatic at the time of presentation.
   b. Enlarged lymphnodes are the most common presenting symptoms.
   c. About 25% of the patients with CLL show autoimmune anaemia only.
   d. IVIG can be used as a short time measure in patient with severe thrombocytopenias.

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Olmecar™ Plus

Olmesartan Medoxomil + Hydrochlorothiazide

Angiotensin II Receptor Blocker+Thiazide Diuretic

PRESENTATION

Olmecar™ Plus 20/12.5 tablet: Each film coated tablet contains Olmesartan Medoxomil INN 20 mg + Hydrochlorothiazide BP 12.5 mg.

INDICATIONS & USES

The usual recommended starting dose of Olmesartan Medoxomil is 20 mg once daily when used as monotherapy in patients who are not volume-contracted. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose may be increased to 40 mg. No initial dosage adjustment is recommended for elderly patients, for patients with moderate to marked renal impairment (creatinine clearance<40 ml/min) or with moderate to marked hepatic dysfunction.

Hydrochlorothiazide is effective in doses between 12.5 mg and 50 mg once daily.

Replacement Therapy : **Olmecar™ Plus**s may be substituted for its titrated components.

Dose Titration by Clinical Effect : The dose of **Olmecar™ Plus** tablet is one tablet once daily. More than one tablet daily is not recommended. **Olmecar™ Plus** tablet may be administered with other antihypertensive agents. A patient whose blood pressure is inadequately controlled by Olmesartan or Hydrochlorothiazide alone may be switched to once daily **Olmecar™ Plus**s tablet. Dosing should be individualized. Depending on the blood pressure response, the dose may be titrated at intervals of 2-4 weeks.

If blood pressure is not controlled by Olmesartan alone, Hydrochlorothiazide may be added starting with a dose of 12.5 mg and later titrated to 25 mg once daily.

If a patient is taking Hydrochlorothiazide, Olmesartan may be added starting with a dose of 20 mg once daily and titrated to 40 mg, for inadequate blood pressure control. If large doses of hydrochlorothiazide have been used as monotherapy and volume depletion or hyponatremia is present, caution should be used when adding Olmesartan or switching to **Olmecar™ Plus** tablet, as marked decreases in blood pressure may occur. Consideration should be given to reducing the dose of Hydrochlorothiazide to 12.5 mg before adding Olmesartan. The antihypertensive effect of OlmecarTM Plus tablet is related to the dose of both components over the range of 10 mg/12.5 mg to 40 mg/25 mg.

Patients with Renal Impairment : The usual regimens of therapy with OlmecarTM Plus tablet may be followed provided the patient's creatinine clearance>30 ml/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so this combination tablet is not recommended.

Patients with Hepatic Impairment : No dosage adjustment is necessary with hepatic impairment.

CONTRAINDICATION

This combination tablet is contraindicated in patients who are hypersensitive to any component of this product. Because of the Hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

SIDE EFFECTS

This combination tablet has been evaluated for safety in 1,243 hypertensive patients. It was well tolerated, with an incidence of adverse events similar to placebo. Events generally were mild, transient and had no relationship to the dose of this combination tablet. Some common side effects include: headache, urinary tract infection, chest pain, back pain, peripheral edema, vertigo, abdominal pain, dyspepsia, gastroenteritis, diarrhoea, SGOT increased, GGT increased, SGPT increased, hyperlipemia, creatine phosphokinase increased, hyperglycemia, arthritis, arthralgia, myalgia, coughing, rash etc.

USE IN PREGNANCY AND LACTATION

Pregnancy : Pregnancy Categories C (first trimester) and D (second and third trimesters). This combination drug should not be used during pregnancy.

Nursing Mothers : It is not known whether Olmesartan is excreted in human milk, but Olmesartan is secreted at low concentration in the milk of lactating rats. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

USE IN CHILDREN

Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTION

Olmesartan Medoxomil : No significant drug interactions were reported in studies in which Olmesartan Medoxomil was coadministered with hydrochlorothiazide, digoxin or warfarin in healthy volunteers.

Hydrochlorothiazide : When administered concurrently the following drugs may interact with thiazide diuretics: alcohol, barbiturates or narcotics, antidiabetic drugs, other antihypertensive drugs, cholestyramine and colestipol resins, corticosteroids, pressor amines (e.g. Norepinephrine), skeletal muscle relaxants (e.g. Tubocurarine), lithium, NSAIDs etc.

OVERDOSAGE

Olmesartan Medoxomil : Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurs.

Hydrochlorothiazide : The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis.

STORAGE CONDITION

Store in a cool and dry place, protect from light and moisture. Keep out of the reach of children.

HOW SUPPLIED

Olmecar™ Plus 20/12.5 tablet: Each box contains 30 tablets in blister pack.

When the need is to treat diarrhoea effectively

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Nitazoxanide 500 mg Tablet &
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Olmecar™

Olmesartan Medoxomil

20 mg
40 mg
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- The most powerful AT_1 Receptor Blocker
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