AUGUST 2011 VOL 18 NO 1 ISSN 1681-5552

# the SQUARE

## healthcare bulletin

Since 1993

- Postpartum Depression
- Influenza
- Unstable Angina
- Drug Allergy

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# Contents

August 2011 VOL 18 NO 1



## *Editorial*

Dear Doctor :

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

In this edition, we have a feature on "Postpartum Depression" which describes the range of physical, emotional, and behavioral changes that many new mothers experience following the delivery of their babies. Symptoms of this condition can range from mild to severe. We focused on "Influenza" which is one of the most common infectious and highly contagious airborne diseases that causes an acute febrile illness and results in variable degrees of systemic symptoms, ranging from mild fatigue to respiratory failure and death. We bring you all the details on "Unstable Angina" which is a medical emergency that accounts for more than millions of hospitalizations annually. Moreover, we have a topic on the "Drug Allergy", the reactions range from irritating or mild side effects such as nausea and vomiting to life-threatening anaphylaxis. We extensively searched for current publications and strive to provide the latest information on those topics. Besides, we have our regular feature on "Product profile" and, "SQUARE in International Business".

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)

# Postpartum Depression

Having a baby is a joyous time for most women. But many women feel sad, afraid, angry or anxious after childbirth. Most new mothers have these feelings in a mild form called **postpartum blues.** Sometimes these feelings are called "baby blues." Postpartum blues almost always go away in a few days. About 10% of new mothers have a more serious problem called **postpartum depression (PPD).** Postpartum depression lasts longer and is more intense. It often requires counseling and treatment. Postpartum depression can occur after any birth, not just the first.

Rarely, an extreme form of postpartum depression known as **postpartum psychosis (PPP)** develops after childbirth. Postpartum depression isn't a character flaw or a weakness. Sometimes postpartum depression is simply part of giving birth.

Postpartum depression is moderate to severe depression in a woman after she has given birth. It may occur soon after delivery or up to a year later. Most of the time, it occurs within the first 4 weeks after delivery.

**Symptoms**

Signs and symptoms of depression after childbirth vary depending on the type of depression

**Baby blues**

Signs and symptoms of the baby blues which last only a few days or weeks may include:

Mood swings

Anxiety

Sadness

Irritability

Crying

Decreased concentration

Trouble sleeping

**Postpartum depression**

Postpartum depression may appear to be the baby blues at first but the signs and symptoms are more intense and longer lasting, eventually interfering with your ability to care for your baby and handle other daily tasks. Signs and symptoms of postpartum depression may include:

Loss of appetite

Insomnia

Intense irritability and anger

Overwhelming fatigue

Loss of interest in sex

Lack of joy in life

Feelings of shame, guilt or inadequacy

Severe mood swings

Difficulty bonding with the baby

Withdrawal from family and friends

Thoughts of harming yourself or the baby

**Postpartum psychosis**

In rare cases, women may experience postpartum psychosis (PPP), a condition that affects about one-tenth of 1 percent of new mothers. Onset is quick and severe and usually occurs within the first two to three weeks following childbirth. Symptoms are similar to those of general psychotic reactions such as delusions and hallucinations and often include:

Physical symptoms : Refusal to eat, inability to cease activity, frantic energy.

Mental symptoms : Extreme confusion, memory loss, incoherence.

Behavioral symptoms : Paranoia, irrational statements, preoccupation with trivial things, attempts to harm herself or baby.

**Causes**

The rapid decline in the levels of reproductive hormones that occurs after delivery is believed to contribute to the development of depression in susceptible women. Although it is tempting to attribute postpartum depression to hormonal decline, several other factors may predispose women to this condition. Stressful life events, 6 past episodes of depression (not necessarily related

**Table-1. Symptoms of Major Depression with Postpartum Onset.***

| |
|---|
| Major depression is defined by the presence of five of the following symptoms, one of which must be depresed mood or decreased interest or pleasure ? |
| Depressed mood, often accompanied or overshadowed by severe anxiety markedly diminished interest or pleasure in activities. |
| Appetite disturbance- usually loss of appetite with weight loss Sleep disturbance- most often insomnia and fragmented sleep, even when the baby sleeps |
| Physical agitation (most commonly) or psychomotor slowing |
| Fatigue, decreased energy |
| Feelings of worthlessness or excessive or inappropriate guilt |
| Decreased concentration or ability to make decisions |
| Recurrent thoughts of death or suicidal ideation |

*From the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV).2 Postpartum depression is defined in the DSM-IV as that which begins within four weeks after delivery.

Symptoms must be present most of the day nearly every day for two weeks. A diagnosis of major depression also requires a decline from the woman's previous level of functioning and substantial impairment.

to childbearing) and a family history of mood disorders, all recognized predictors of major depression in women 6 are also predictors of postpartum depression. The likelihood of postpartum depression does not appear to be related to a woman's educational level, the sex of her infant, whether or not she breast-feeds, the mode of delivery or whether or not the pregnancy was planned.

There is no single cause for postpartum depression. Physical, emotional and lifestyle factors may all play a role.

**Physical changes.** After childbirth, a dramatic drop in estrogen and progesterone may contribute to postpartum depression. The hormones produced by the thyroid gland also may drop sharply which can leave her feeling tired, sluggish and depressed. Changes in her blood volume, blood pressure, immune system and metabolism can lead to fatigue and mood swings.

**Emotional factors.** When she is sleep deprived and overwhelmed, she may have trouble handling even minor problems. She may be anxious about her ability to care for a newborn. She may feel less attractive or struggle with her sense of identity. She may feel that she has lost control over her life. Any of these factors can contribute to postpartum depression.

**Lifestyle influences.** Many lifestyle factors can lead to postpartum depression including a demanding baby or older siblings, difficulty breast-feeding, exhaustion, financial problems and lack of support from partner or other loved ones.

**Risk factors**

Postpartum depression can develop after the birth of any child, not just the first. The risk increases if :

- ❑ She has a history of depression, either during pregnancy or at other times
- ❑ She had postpartum depression after a previous pregnancy
- ❑ She has experienced stressful events during the past year, including illness, job loss or pregnancy complications
- ❑ She is experiencing marital conflict
- ❑ She has a weak support system
- ❑ The pregnancy is unplanned or unwanted
- ❑ The risk of postpartum psychosis is higher for women who have bipolar disorder.

**When to Suspect Postpartum Depression**

A new mother may be developing or already have postpartum depression if she has any of the following signs or symptoms:

- ❑ The baby blues do not start to fade after about 1 week or if the feelings get worse.
- ❑ Strong feelings of depression and anger come 1–2 months after childbirth.
- ❑ Feelings of sadness, doubt, guilt or helplessness seem to increase each week and get in the way of normal functions.
- ❑ She is not able to care for herself or her baby.
- ❑ She has trouble doing tasks at home or on the job.
- ❑ Her appetite changes.

Things that used to bring her pleasure no longer do.

Concern and worry about the baby are too intense or interest in the baby is lacking.

Anxiety or panic attacks occur. She may be afraid to be left alone in the house with the baby.

She fears harming the baby. These feelings are almost never acted on by women with postpartum depression but they can be scary. These feelings may lead to guilt which makes the depression worse.

She has thoughts of self-harm or suicide.

A new mother having any of these signs or symptoms should take steps right away to get help.

**Birth-related post traumatic stress disorder (PTSD)**

After childbirth, women may also experience post traumatic stress disorder (PTSD). PTSD includes two key elements : (1) experiencing or witnessing an event involving actual or threatened danger to the self or others and (2) responding with intense fear, helplessness or horror. Symptoms of birth-related PTSD may include :

Obsessive thoughts about the birth

Feelings of panic when near the site where the birth occurred

Feelings of numbness and detachment

Disturbing memories of the birth experience

Nightmares

Flashbacks

Sadness, fearfulness, anxiety or irritability

**Diagnosis**

Some of the most common symptoms of PPD are depressed mood, sleep disturbances, weight loss, anxiety or irritability, loss of energy, lack of concentration, feelings of worthlessness or guilt and thoughts of suicide or death. Because of the close symptomatic similarities between PPD and major depression, the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* does not classify PPD as a separate diagnosis. Instead, a "postpartum-onset specifier" is used to describe mood disorders that occur within four weeks of delivery. The DSM-IV uses the same criteria for diagnosing major depression as it does for PPD.

It is important for health care providers to distinguish between the signs of PPD and the normal mood fluctuations women experience postpartum when making a definitive diagnosis of PPD. For example, it is normal for a woman to be exhausted and irritable when her newborn nurses every few hours and awakens

multiple times throughout the night; a woman experiencing these symptoms when the baby is five months old and sleeping through the night should be evaluated for PPD.

Screening all women for the signs and symptoms of depression in the postpartum period is the most effective way to identify and treat the disorder before it progresses. Providers should screen for PPD at a woman's first postpartum follow-up visit and again at six weeks. The Edinburgh Postnatal Depression Scale (EPDS) is a 10-item questionnaire designed to identify PPD; with 100% sensitivity and 95% specificity in multiple studies, this tool is utilized by physicians worldwide. Data on the success of the EPDS are limited. Other screening tools are the Postpartum Depression Screening Scale and the Beck Depression Inventory.

**Evaluation and Differential Diagnosis**

If the patient has considered a plan to act on suicidal thoughts or has thoughts about harming her infant, provisions for safety and urgent referral for psychiatric care are recommended. Women who have major functional impairment (as evidenced by the avoidance of family or friends, an inability to attend to hygiene or an inability to care adequately for the infant) and those with coexisting substance abuse are also candidates for rapid referral. Women who report depressive symptoms without suicidal ideation or major functional impairment (or score between 5 and 9 on the Edinburgh Postnatal Depression Scale) should be evaluated again two to four weeks later in order to determine whether an episode of depression has evolved or whether symptoms have subsided.

A careful history taking and a physical examination are warranted in all women with postpartum depression. Thyroid function should be assessed, since both hypothyroidism and hyperthyroidism are more frequent during the postpartum period and may contribute to mood changes. However, in women with hyperthyroidism or hypothyroidism, treatment of both thyroid and depressive disorders is usually required.

Postpartum depression must be distinguished from the "baby blues," which occur in the majority of new mothers. In this syndrome, symptoms such as weeping, sadness, irritability, anxiety and confusion occur, peaking around the fourth day after delivery, and resolving by the tenth day. This transient mood disturbance does not consistently affect the woman's ability to function.

Postpartum psychosis represents a psychiatric emergency that requires immediate intervention because of the risk of infanticide and suicide. Onset usually occurs within the first two weeks after delivery. This disorder differs from other psychotic episodes because it usually involves extreme disorganization of thought, bizarre behavior, unusual hallucinations (which may be visual, olfactory or tactile) and delusions, all of which suggest an organic cause. Treatments for postpartum psychosis have been discussed in detail elsewhere.

Postpartum psychosis is usually a manifestation of bipolar disorder. A depressive episode (with or without psychotic features) can occur during the course of bipolar disorder. Therefore, all patients with postpartum depression should be screened with the following questions: "Have you ever had four continuous days when you were feeling so good, high, excited or 'hyper' that other people thought you were not your normal self or you got into trouble?" and "Have you experienced four continuous days when you were so irritable that you found yourself shouting at people or starting fights or arguments?" Positive responses to these questions necessitate psychiatric referral.

**Complications**

Left untreated, postpartum depression can interfere with mother-child bonding and cause family distress. Children of mothers who have untreated postpartum depression are more likely to have behavioral problems, such as sleeping and eating difficulties, temper tantrums and hyperactivity. Delays in language development are common as well.

Untreated postpartum depression can last up to a year or longer. Sometimes untreated postpartum depression becomes a chronic depressive disorder. Even when treated, postpartum depression increases a woman's risk of future episodes of major depression.

**Treatment**

**Baby blues**

The baby blues usually fade on their own within a few days to weeks. In the meantime, get as much rest as you can. Accept help from family and friends. Connect with other new moms. Avoid alcohol, which can make mood swings worse. If there is an underactive thyroid, your doctor may prescribe thyroid medication.

While optimal treatment strategies are still being researched, effective management of PPD includes both nonpharmacologic and pharmacologic interventions. Women with mild-to-moderate symptoms of PPD should try nonpharmacologic treatments, such as psychosocial therapy. In addition to being effective, these mechanisms are desirable for women who want help but wish to avoid using medications while they are breast-feeding. Interpersonal therapy (IPT), a type of psychotherapy, focuses on a woman's relationships and the role transitions that occur after the birth of a child. A study conducted in 2000 found that 12 weeks of IPT were more effective than no treatment at improving social adjustment and decreasing PPD symptoms. Cognitive-behavioral therapy helps a woman identify negative thoughts, beliefs and behaviors that are inaccurate or dysfunctional and learn to replace them with more positive, realistic thought processes. Other nonpharmacologic treatments for PPD are group therapy, nondirective counseling, light therapy, partnersupport counseling and peer support groups.

Pharmacologic intervention is warranted when a woman's PPD

symptoms become moderate-to-severe or when the woman does not respond to nonpharmacologic therapy alone.

***Antidepressants :*** Although benzodiazepines are a useful adjunct for the anxiety and agitation associated with PPD, antidepressants are recommended to treat the core symptoms of the disorder. While there are many studies reporting the effectiveness of antidepressants for treating depression, almost no data (i.e. randomized, placebo controlled trials) exist as to the efficacy of these medications for the treatment of PPD specifically. Because of this, antidepressants are often used for PPD based on study results for depression in the general population.

Due to their effectiveness, low incidence of side effects, safety in the event of overdose and once daily dosage formulations, selective serotonin reuptake inhibitors (SSRIs) are considered first line agents for the treatment of PPD. Although the side effect profile and overdose severity of the tricyclic antidepressants (TCAs) are greater than those of the SSRIs, TCAs have been shown to improve the symptoms of PPD also. One double-blind trial of nortriptyline (a TCA) and sertraline (an SSRI) found that 109 women divided between the two drugs had the same response and remission rate for PPD at four, eight and 24 weeks. SSRIs and TCAs are used most often but other antidepressants are available to treat PPD (e.g. serotonin norepinephrine reuptake inhibitors, dopamine reuptake inhibitors). Doses, side effects and breast-feeding recommendations for the most frequently prescribed antidepressant agents are summarized in table.

Most women show signs of improvement within two to six weeks of medication initiation. If no improvement is noted or symptoms worsen after two weeks, the physician should consider increasing the dosage or switching to a different agent. Antidepressant treatment should continue for nine to 12 months to achieve full remission and minimize the chance of relapse.

**Table : Antidepressant Therapy for PPD**

| Drug | Dosage | Side Effects | Use During Breast Feeding |
|---|---|---|---|
| | | **SSRIs** | |
| Sertraline | 50-200 mg/day | Headache, nausea, insomnia, sexual daysfunctions, dizziness, treamor | No AEs reported |
| Paroxetine | 20-60 mg/day | Same as sertraline | No AEs reported |
| Fluoxetine | 20-80 mg/day | Same as sertraline | Drug, active metabolites have long elimination halflives; crying, sleep disturbance, vomiting, watery stools in exposed infants; monitor infant blood levels at 6 wk to rule out accumulation |
| Fluvoxamine | 100-300 mg/day | Same as sertraline | No AEs reported |
| Citalopram | 20-40 mg/day | Somnolence, insomnia, nausea diaphoresis, agitation | No AEs reported nursing infants |
| | | **SNRIs** | |
| Venlafaxine | 75-300 mg/day | Headache, dizziness, insomnia, nausea, nervousness, sustained HT | Undetectable/low serum levels of drug; metabolites usually measurable; levels similar to adult levels in some infants |
| Duloxetine | 40-60 mg/day | Nausea, dizziness, headche, insomnia, diarrhea, dry mouth | Unknown |
| | | **TCAs** | |
| Nortriptyline | 75-150 mg/day | Dry mouth, blurred vision, sedation, constipation, OH, weight gain | No AEs reported |
| Imipramine | 50-300 mg/day (outpatients: max 150 mg/day) | Same as nortriptyline | Unknown |
| Desipramine | 75-300 mg/day | Same as nortriptyline | No AEs reported |
| Amitriptyline | 50-300 mg/day (outpatients: max 150 mg/day) | Same as nortriptyline | Unknown |
| | | **Other** | |
| Bupropion | 150-450 mg/day | Headache, nausea, insomnia, agitation | Unknown |
| Nefazodone | 300-600 mg/day | OH, dry mouth, nausea, somnolence | No published data on serum levels in infants; sedation poor feeding in premature infants |
| Mirtazapine | 15-45 mg/day | Somnolence, dry mouth, weight gain, increased cholesterol/TG levels | Unknown |

*PPD: postpartum depression; SSRI : selective serotonin reuptake inhibitor; AE: adverse event: SNRI : serotonin norepinepbrine reuptake inhibitor; HT: hypertension> TCA tricyclic antidepressant; max: maximum; TG: triglyceride.*

A major factor to consider in deciding whether to treat PPD with antidepressants is whether the patient is breast-feeding. It is necessary to inform patients that all antidepressants are excreted into breast milk and that studies have found detectable drug concentrations in the plasma of some breastfed infants. It is important to note, however, that these infants were found to tolerate exposure without harm and that instances of toxicity were extremely rare. While data on the adverse effects of antidepressants in infants during breast - feeding are limited, several studies have concluded that the SSRIs sertraline, paroxetine, and fluvoxamine have the least transmission to infants through breast milk. Physicians should discuss with their patients the risks and benefits of antidepressant use while breast - feeding and help them decide which course of therapy is most appropriate for them to ensure a successful recovery.

***Other Pharmacologic Agents :*** Antidepressants remain the standard for the treatment of moderate-to-severe PPD. However, although supportive data are limited, hormonal therapy, omega-3 fatty acids and anxiolytics also have been used as alternatives for treating PPD.

**Postpartum psychosis**

Postpartum psychosis requires immediate treatment, often in the hospital.

After safety is assured, a combination of medications - such as antidepressants, antipsychotic medications and mood stabilizers may be used to control her signs and symptoms. Sometimes electroconvulsive therapy (ECT) is recommended as well. The chemical changes triggered by the electrical currents can reduce the symptoms of depression, especially when other treatments have failed or when you need immediate results. Mothers who experience PPP are highly likely to suffer from it again following their next pregnancy.

Treatment for postpartum psychosis can challenge a mother's ability to breast-feed. Separation from the baby makes breastfeeding difficult and some medications used to treat postpartum psychosis aren't recommended for women who are breast-feeding.

**Prevention**

If she has a history of depression-especially postpartum depression-she should mention it to the doctor as soon as she finds out she is pregnant. The doctor must monitor her closely for signs and symptoms of depression. Sometimes mild depression can be managed with support groups, counseling or other therapies. In other cases, antidepressants are recommended-even during pregnancy.

After the baby is born, it is recommended to have an early postpartum checkup to screen for signs and symptoms of postpartum depression. The earlier postpartum depression is detected, the earlier treatment can begin.

**Lifestyle and home remedies**

Postpartum depression isn't generally a condition that a woman can treat on her own but she can do some things for herself that build on her treatment plan. In fact, taking good care of herself can help speed her recovery.

**Healthy lifestyle choices.** Rest as much as she can. Physical activity (such as a walk with her baby, in her daily routine) should be included. Healthy foods-plenty of fruits, vegetables and whole grains should be taken. Alcohol should be avoided.

**Setting realistic expectations.** It is important not to pressure her to do everything. Expectations for the perfect household should be reduced. Asking for help when needed is important.

**Avoiding isolation.** Talking with her family and friends about how she is feeling. She may ask other mothers about their experiences.

**Alternative medicine:** Little research has been done on complementary and alternative therapies for postpartum depression. The following may be considered weighing the benefits and risks of specific therapies, such as:

a. **Acupuncture.** Acupuncture helps promote deep relaxation and sometimes even sleep. This may help relieve the fatigue that accompanies postpartum depression.

b. **Omega-3 fatty acids.** Omega-3 fatty acids are known to support infant brain development during pregnancy. Some research suggests that omega-3 fatty acids whether eaten in fish and other seafood or taken as a nutritional supplement may help relieve postpartum depression as well.

c. **Massage therapy.** Some studies suggest that massage therapy may be helpful for postpartum depression.

d. **Creative arts.** Art, music and drama therapy have been suggested as possible ways to relieve postpartum depression, perhaps by providing a supportive, relaxed environment, offering new ways of expression or encouraging positive behavior changes.

Some studies suggest that the herb St. John's wort may be helpful for mild to moderate depression, although there's been no research published on St. John's wort and postpartum depression specifically. It's best to avoid St. John's wort in breast-feeding women. St. John's wort may cause colic, drowsiness or lethargy in a nursing baby.

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## Influenza (Flu)

Influenza or flu, is a respiratory tract infection caused by several flu viruses. Flu viruses are classified as types A, B and C; type A has a number of subtypes. The flu is not the same as the common cold, nor it is related to what is commonly called the "stomach flu."

### Seasonal Flu

Seasonal flu is the term used to refer to the flu outbreaks that occur yearly, mainly in the late fall and winter. It is estimated that between 5 and 20 percent of Americans come down with the flu every flu season.

### Pandemic Flu

Pandemic flu refers to particularly virulent strains of flu that spread rapidly from person to person to create a world-wide epidemic (pandemic).

### Avian (Bird) Flu

In nature, the flu virus also occurs in wild aquatic birds such as ducks and shore birds. It does not normally spread from birds to humans. However, pigs can be infected by bird influenza (as well as by the form of influenza that affects humans) and can pass on the flu to humans. In 1997, it was discovered that a virulent bird influenza had skipped the pig step and had infected humans directly, causing a number of deaths in Asia.

These instances of bird flu in humans have raised concerns that if this type of flu could at some point be transmitted between people, a new pandemic would occur. Thus, the term bird flu or avian flu is currently being used to refer to a possible pandemic flu.

### Overview

Influenza, commonly called "the flu," is an illness caused by RNA viruses that infect the respiratory tract of many animals, birds and humans. In most people, the infection results in the person getting fever, cough, headache and malaise; some people also may develop a sore throat, nausea, vomiting and diarrhea. The majority of individuals has symptoms for about one to two weeks and then recovers with no problems. However, compared with most other viral respiratory infections, such as the common cold, influenza (flu) infection can cause a more severe illness with a mortality rate of about 0.1% of people who are infected with the virus.

The above is the usual situation for the yearly occurring "conventional" or "seasonal" flu strains. However, there are situations in which some flu outbreaks are severe. These severe outbreaks occur when the human population is exposed to a flu strain against which the population has little or no immunity because the virus has become altered in a significant way. Unusually severe worldwide outbreaks (pandemics) have occurred several times in the last hundred years since influenza virus was identified in 1933. By an examination of preserved tissue, the worst influenza pandemic (also termed the Spanish flu) occurred in 1918 when the virus caused between 40-100 million deaths worldwide, with a mortality rate estimated to range from 2%-20%.

In April 2009, a new influenza strain against which the world population has little or no immunity was isolated from humans in Mexico. It quickly spread throughout the world so fast that the WHO declared this new flu strain (termed novel H1N1 influenza A swine flu, often shortened to H1N1 or swine flu) as the cause of a pandemic on June 11, 2009. This was the first declared flu pandemic in 41 years.

### The Flu Virus

Influenza viruses are classified as type A, B or C. Type A is the most common and causes most of the serious epidemics. It infects many animals, such as ducks, chickens and pigs, as well as humans. Type B can cause epidemics but these are usually milder than type A influenza. Type C has never been associated with an epidemic. Influenza is not the same as the common cold. Similarly, "stomach flu" is not influenza. The H1N1 influenza virus or "swine flu," is a new type A influenza virus, probably resulting from an abrupt change in virus structure. It is so different that no one knows how severe it will be in the general population; this leads to concern that it may be particularly virulent. It is currently causing global (pandemic) disease. Among many subtypes of influenza A viruses, currently influenza A(H1N1) and A(H3N2) subtypes are circulating among humans. Influenza viruses circulate in every part of the world. Type C influenza cases occur much less frequently than A and B. That is why only influenza A and B viruses are included in seasonal influenza vaccines.

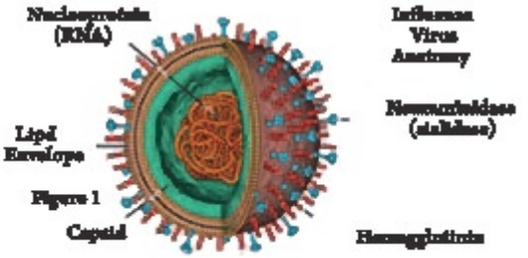
Influenza viruses continually change over time, usually by mutation. This constant changing often enables the virus to evade the immune system of the host (humans, birds and other animals) so that the host is susceptible to changing influenza virus infections throughout life. Type A viruses are divided into types based on differences in two viral surface proteins called the hemagglutinin (H) and the neuraminidase (N). There are 16 known H subtypes and nine known N subtypes. These surface proteins can occur in many combinations. When spread by droplets or direct contact, the virus, if not killed by the host's

# Influenza (Flu)

immune system, replicates in the respiratory tract and damages host cells. In people who are immune compromised (for example, pregnant individuals, infants, cancer patients, asthma patients, people with pulmonary disease and many others), the virus can cause viral pneumonia or stress the individual's system to make them more susceptible to bacterial infections, especially bacterial pneumonia. Both pneumonia types, viral and bacterial, can cause severe disease and sometimes death. The incubation period of influenza ranges from 18-72 hours. In addition, several serious viruses, including adenoviruses, enteroviruses and paramyxoviruses, may initially cause influenza like symptoms. The early presentation of mild or moderate cases of flavivirus infections (e.g. dengue) may initially mimic influenza.

### Antigenic Shift and Drift

Influenza type A viruses undergo two kinds of changes. One is a series of mutations that occurs over time and causes a gradual evolution of the virus. This is called antigenic 'drift.' The other




kind of change is an abrupt change in the hemagglutinin and/or the neuraminidase proteins. This is called antigenic 'shift.' In this case, a new subtype of the virus suddenly emerges. Type A viruses undergo both kinds of changes; influenza type B viruses change only by the more gradual process of antigenic drift and therefore do not cause pandemics. The U.S. Centers for Disease Control and Prevention (CDC) has indicated that novel H1N1 swine flu has an RNA genome that contains five RNA strands derived from various swine flu strains, two RNA strands from bird flu strains and only one RNA strand from human flu strains. They suggest mainly antigenic shifts over about 20 years have led to the development of novel H1N1 flu virus.

### Transmission

Influenza is transmitted from person to person by droplets when infected people cough or sneeze. It is also possible to become infected after touching a surface that has been contaminated by someone who has flu. Those living in crowded conditions or in schools are at greatest risk of infection. People are infectious from one day before symptoms develop until up to five days after becoming sick.

**Common Cold vs Flu**

| Symptoms | Common Cold | Flu |
|---|---|---|
| Headache: | Rare | Common |
| Chest discomfort: | Mild to moderate | Often severe |
| Sneezing: | Common | Rare |
| Coughing: | Hacking, productive cough | Dry, unproductive cough |
| Sudden symptoms: | Appear gradually | Can appear within 3-6 hours |
| Causative Organism: | Adenoviruses, coronaviruses or rhinoviruses | Influenza virus |
| Chills: | Rare | Common |
| Fatigue: | Mild | Moderate to severe |
| Aches: | Slight | Usual and often severe |
| Fever: | Rare | Usually present |
| Vaccination possible: | No | Yes |
| Severity: | Usually does not cause severe health problems | Serious health problems, such as pneumonia, bacterial infections, or hospitalizations can occur. |
| Sore throat: | Common | Rare |
| Stuffy nose: | Common | Rare |
| Can be diagnosed: | No | Yes |

**Common Cold vs Flu**

| Symptoms | Cold | Flu |
|---|---|---|
| Fever | Rare | Characteristic, high (100-102 degrees F); lasts three to four days |
| Headache | Rare | Prominent |
| General Aches, Pains | Slight | Usual; often severe |
| Fatigue, Weakness | Quite mild | Can last up to two to three weeks |
| Extreme Exhaustion | Never | Early and prominent |
| Stuffy Nose | Common | Sometimes |
| Sneezing | Usual | Sometimes |
| Sore Throat | Common | Sometimes |
| Chest Discomfort | Mild to moderate | Common; can become severe |
| Cough | hacking cough | Bronchitis, pneumonia; can be life-threatening |
| Complications | Sinus congestion or earache | Annual flu shot or FluMist |
| Prevention | Good hygiene | Antiviral drugs (Tamiflu or or Relenza) within 24-48 hours of onset |
| Treatment | Only temporary relief of symptoms | |

### Symptoms

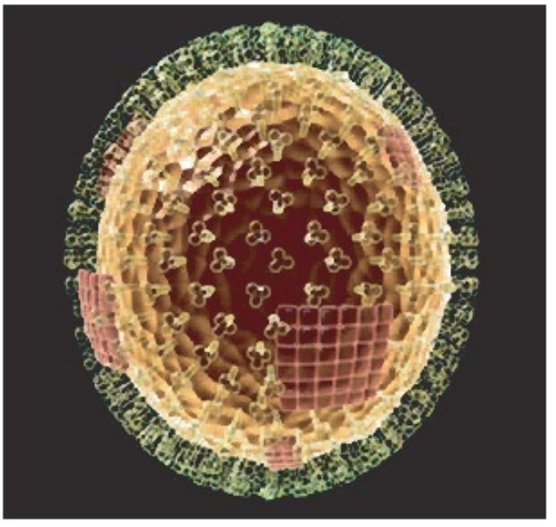
Typical clinical features of influenza include :

- ☐ fever (usually 100 F-103 F in adults and often even higher in children)
- ☐ respiratory symptoms such as
  - cough
  - sore throat
  - runny or stuffy nose

- headache
- muscle aches and
- fatigue, sometimes extreme.

Although nausea, vomiting and diarrhea can sometimes accompany influenza infection, especially in children, gastrointestinal symptoms are rarely prominent. The term "stomach flu" is a misnomer that is sometimes used to describe gastrointestinal illnesses caused by other microorganisms. Novel H1N1 infections cause more nausea, vomiting and diarrhea than the conventional (seasonal) flu viruses.

Most people who get the flu recover completely in one to two weeks but some people develop serious and potentially lifethreatening medical complications, such as pneumonia. In an



average year, influenza is associated with about 36,000 deaths nationwide and many more hospitalizations. Flu related complications can occur at any age; however, the elderly and people with chronic health problems are much more likely to develop serious complications after the conventional influenza infections than are younger, healthier people. However, the novel H1N1 virus has initially developed a different pattern of infection. Unfortunately, the pattern of infection is similar to that of the 1918 "Spanish flu" pandemic in which young people (pregnant individuals, infants, teens and adults through age 49) are the most susceptible populations worldwide.

**Risk Group**

Yearly influenza epidemics can seriously affect all age groups but the highest risk of complications occur among children younger than age two, adults age 65 or older and people of any age with certain medical conditions, such as chronic heart, lung, kidney, liver, blood or metabolic diseases (such as diabetes) or weakened immune systems.

**Laboratory Diagnosis**

A number of tests such as Viral culture, Immunofluorescence DFA Antibody Staining, RT-PCR, Serology, Enzyme Immuno Assay (EIA) can help in the diagnosis of influenza but not routinely done. Rapid diagnostic kit is available and is able to give the results within 15 minutes but not required to be done on all patients. During a respiratory illness outbreak in a closed setting (e.g. hospitals, nursing home, school, summer camp) however, testing for influenza can be very helpful in determining if influenza is the cause of the outbreak.

Preferred respiratory samples for influenza testing include nasopharyngeal or nasal swab and nasal wash or aspirate, depending on which type of test is used. Samples should be collected within the first 4 days of illness. Rapid influenza tests provide results within 15 minutes or less; viral culture provides results in 3-10 days. Most of the rapid tests are approximately 50%-70% sensitive for detecting influenza and approximately greater than 90% specific. Therefore, false negative results are more common than false positive results, especially during peak influenza activity. Serological testing results for human influenza on a single serum specimen is not interpretable and is not recommended.

During outbreaks of respiratory illness when influenza is suspected, some respiratory samples should be tested by both rapid tests and by viral culture. The collection of some respiratory samples for viral culture is essential for determining the influenza A subtypes and influenza A and B strains causing illness and for surveillance of new strains that may need to be included in the next year's influenza vaccine. During outbreaks of influenza-like illness, viral culture also can help identify other causes of illness.

**Medical Treatment**

As with other diseases, prevention of influenza is the most effective strategy. It is recommended that all, those are in highrisk groups, including all health care personnel, should be vaccinated. Antiviral drugs are important in the management of seasonal influenza and critical to pandemic planning. Although several other classes of anti-influenza compounds exist, the neuraminidase (NA) inhibitors are currently the only option in most clinical settings. These drugs, zanamivir and oseltamivir, prevent the release of newly replicated influenza virions from infected cells. They are highly effective when used for treatment of seasonal influenza early in the course of infection or for prevention when given soon after exposure.

Treatment strategies for avian influenza infections in humans are still provisional owing to inadequate clinical data. As predicted by molecular studies, resistance to the NA inhibitors is now emerging, although at a level less significant than adamantane resistance. NA inhibitor resistance is a cause for concern if indeed some mutant strains of avian influenza are transmissible and

pathogenic. In the near term, appropriate use of the available NA inhibitors will be of major benefit in lessening morbidity and mortality due to influenza infection. Priorities include developing appropriate formulations and guidelines for use of these drugs in children and people infected with avian influenza, study of the mechanisms and clinical significance of drug resistance and identification of new antiviral therapies that target different points in the viral life cycle in order to limit the effect of emerging drug resistance.

**Efficacy and Timing of Treatment**

Zanamivir and oseltamivir are effective for both prophylaxis and treatment of influenza A and B infection. Several large treatment trials in widely diverse geographical locations showed that when otherwise healthy adults with influenza were treated with zanamivir or oseltamivir within 36–48 h after onset of illness, a one - to - two day decrease in symptomatic illness occurred. Treatment also decreases the number and severity of lower respiratory tract complications and reduces the use of antibiotics. However, the positive effects of treatment are greatly enhanced if treatment is started early. Because replication of influenza virus in the respiratory tract peaks between 24 and 72 h after onset of illness, the earlier the administration of the drug, the shorter the duration of the fever and the faster the return to baseline health.

In children, both zanamivir and oseltamivir shorten the duration and severity of influenza symptoms by 1.5 days if started within 48 h after onset of illness and presumably would be even more effective if initiated earlier. Oseltamivir may currently be used to treat influenza in children aged one year and older, whereas the use of zanamivir is reserved for children five years and older because of the need for an inhaler device. Given the lack of therapeutic options for infants, the evaluation of the pharmacokinetics and tolerance of oseltamivir in infants less than one year old is of critical importance. Of note, however, especially in young children, oseltamivir is much less effective as a treatment for influenza B than for influenza A virus infection. Zanamivir binds more strongly than oseltamivir in the active site of the influenza B virus NA and this affinity difference may affect clinical efficacy. The use of oseltamivir against influenza. Binfection in young children may need to be reconsidered and the options of either increasing the dosage of oseltamivir for influenza B or using zanamivir are worth considering.

Zanamivir and oseltamivir are both 70%– 90% effective in preventing clinical influenza in healthy adults, when used either as postexposure prophylaxis for close contacts such as household members or as seasonal prophylaxis in the community. Oseltamivir may be used for protection of elderly persons in residential institutions, where a 92% reduction in the incidence of influenza was observed even though most of the elderly residents had been appropriately vaccinated.

**Resistance**

A strength of the NA inhibitors oseltamivir and zanamivir over the adamantanes is that they are less prone to selecting for resistant influenza viruse. Little spontaneous resistance to NA inhibitors has been documented, no spontaneously resistant influenza viruses were identified prior to the introduction of the drugs and no virus resistant to zanamivir has yet been isolated after the treatment of immunocompetent people. The recent emergence of oseltamivir resistant variants is therefore a matter of great concern. Beginning in 2004, resistance to oseltamivir in strains of influenza A has been gradually growing more common. Because the clinical relevance and transmissibility of the resistant variants have been unknown, planning for epidemic and pandemic influenza thus far has discounted the issue of oseltamivir resistance. However, recently, influenza B viruses with decreased sensitivity to oseltamivir and zanamivir were isolated from individuals in Japan who had not been treated with antiviral medications. The pattern of virus isolation strongly suggested that person-to-person transmission of these resistant viruses had occurred, either within families or in the community. The evidence that some NA inhibitor–resistant influenza virus variants are indeed transmissible and are vigorous pathogens may require a change in treatment guidelines.

**Complication**

Complications of influenza may include Primary viral pneumonia, Secondary bacterial pneumonia, Combined bacterial-viral pneumonia, Execerbaion of chronic pulmonary disease, Croup, Cardiac complications (most notably Heart Failure), Central nervous system complications (i.e. seizures, acute encephalitis and post infectious encephalopathy), Reye's syndrome, Myositis, Toxic shock syndrome etc. To prevent complication and to minimize death early recognition and treatment is necessary especially in immune-compromised people. Vaccination may prevent from flu attack but due to the continuous evolving nature of the influenza virus, vaccination may not be the ultimate protection. It is important to stay updated and to follow the precautions about health and hygiene and thus flu can be prevented in a greater way.

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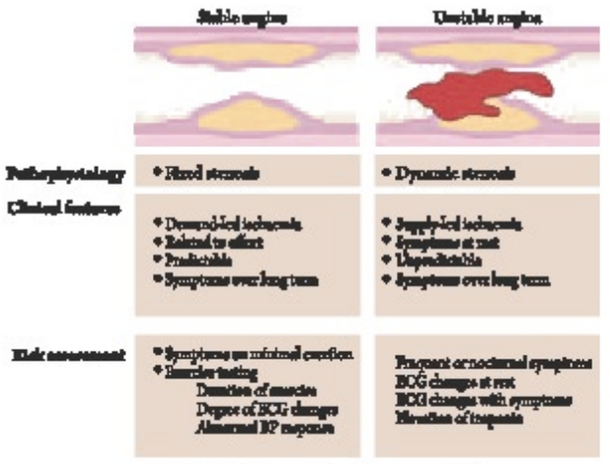
# Unstable Angina



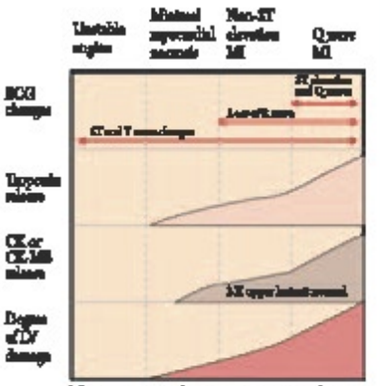
## Introduction

Unstable Angina (UA) is a medical emergency. It accounts for more than millions of hospitalization annually; 6 to 8 percent of patients with this condition have nonfatal myocardial infarction or die within the first year after diagnosis. The traditional term of unstable angina was first used 3 decades ago and was meant to signify the intermediate state between myocardial infarction (MI) and the more chronic state of stable angina. The old term, pre-infarction angina conveys the clinical intent of intervening to attenuate the risk of myocardial infarction or death. Patients with this condition have also been categorized according to their presentation, diagnostic test results or course over time; these categories include new onset angina, accelerating angina, rest angina, early post-infarct angina and early postrevascularization angina. Various definitions of unstable angina have been proposed, simply Unstable Angina is a clinical syndrome characterized by new onset or rapidly worsening angina (crescendo angina), angina on minimal exertion or angina at rest. It is characterized by at least one of the following features: (1) occurs at rest or minimal exertion and usually lasts >20 minutes (2) it is severe (described as frank pain) and of new onset (i.e. within the prior 4–6 weeks) and/or (3) occurs with a crescendo pattern (i.e. distinctly more severe, prolonged or frequent than previously).




Pathophysiology, clinical features and risk assessment of patients with stable or unstable angina

The condition (UA) shares common pathophysiological mechanisms with acute myocardial infarction. 50% of people with unstable angina will have evidence of myocardial necrosis based on elevated cardiac serum markers such as creatine kinase isoenzyme (CK)-MB and troponin T or I, and thus have a diagnosis of NSTEMI. So, recently the term "acute coronary syndromes" has been used to describe the spectrum of conditions collectively, that includes unstable angina, non–Q-wave myocardial infarction (which generally presents without ST-segment elevation) and Q-wave myocardial infarction (which generally presents with ST-segment elevation). Patients with unstable angina and those with non–Q-wave myocardial infarction often present in a similar manner and the distinction between the two conditions can be made only many hours or days later, when the results of cardiac enzyme tests become available.




The spectrum of acute coronary syndromes.

### Classification of Unstable Angina

In 1989, Braunwald devised a classification system to ensure uniformity of categorization as well as diagnostic and prognostic information. The classification is conceptually useful because it factors in the clinical presentation (new or progressive vs rest angina), context (primary, secondary or post–myocardial infarction) and intensity of anti-anginal therapy. Patients in class I have new or accelerated exertional angina, whereas those in class II have sub-acute (>48 h since last pain) or class III acute (<48 h since last pain) rest angina. The clinical circumstances associated with unstable angina are categorized as (A) secondary (anemia, fever, hypoxia, tachycardia or thyrotoxicosis)) (B) primary or (C) postinfarction (<2 wk after infarction). Intensity of anti-anginal therapy is subclassified as (1) no treatment, (2) usual oral therapy and (3) intense therapy, such as intravenous nitroglycerin.

| Characteristic | Class/Category | Details |
|---|---|---|
| Severity | I | Symptoms with exertion |
| | II | Subacute symptoms at rest (2-30 d prior) |
| | III | Acute symptoms at rest (within prior 48 h) |
| Clinical precipitating factor | A | Secondary |
| | B | Primary |
| | C | Postinfarction |
| Therapy during symptoms | 1 | No treatment |
| | 2 | Usual angina therapy |
| | 3 | Maximal therapy |

Braunwald Classification of Unstable Angina

The Canadian Cardiovascular Society Grading System for effort related angina is widely used since it is a simple and practical classification that is often used to describe symptom severity. It is as follows:

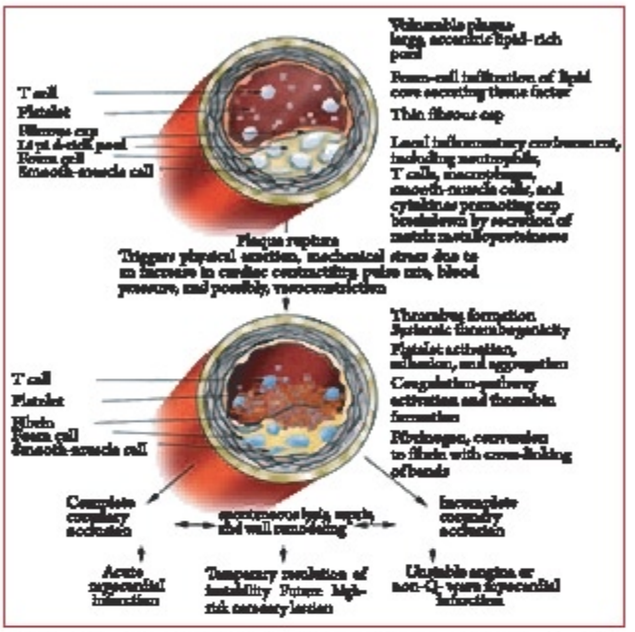
- **Grade I :** Angina with strenuous, rapid or prolonged exertion. (Ordinary physical activity such as climbing stairs does not provoke angina.)
- **Grade II :** Slight limitation of ordinary activity. (Angina occurs with postprandial, uphill or rapid walking; when walking more than 2 blocks of level ground or climbing more than one flight of stairs; during emotional stress or in the early hours after awakening.)
- **Grade III :** Marked limitation of ordinary activity. (Angina occurs with walking 1-2 blocks or climbing a flight of stairs at a normal pace.)
- **Grade IV :** Inability to carry on any physical activity without discomfort. (Rest pain occurs.)

**Pathogenesis**

UA/NSTEMI is most commonly caused by a reduction in oxygen supply and/or by an increase in myocardial oxygen demand superimposed on an atherosclerotic coronary plaque, with varying degrees of obstruction. Four pathophysiologic processes that may contribute to the development of UA/NSTEMI have been identified: (1) Plaque rupture or erosion with superimposed non-occlusive thrombus, (believed to be the most common cause) (2) progressive mechanical obstruction (e.g. rapidly advancing coronary atherosclerosis or restenosis) (3) Dynamic obstruction e.g. coronary spasm and (4) secondary UA related to increased myocardial oxygen demand and/or decreased supply (e.g. tachycardia, anemia). Secondary disorders cause ischemia by increasing myocardial oxygen demand (e.g. thyrotoxicosis, cocaine, severe illness, physiologic stress) or by decreasing oxygen supply (e.g. hypoxemia, anemia, hypotension). Such causes must be investigated because most of these conditions are reversible. More than one of these processes may be involved.

**Plaque rupture/disruption**

Accumulation of lipid-laden macrophages and smooth muscle cells, so-called foam cells, occurs within atherosclerotic plaques. The oxidized low density lipoprotein cholesterol (LDL-C) in foam cells is cytotoxic, procoagulant and chemotactic. As the atherosclerotic plaque grows, production of macrophage proteases and neutrophil elastases within the plaque can cause thinning of the fibromuscular cap that covers the lipid core. Increasing plaque instability coupled with blood-flow shear and circumferential wall stress lead to plaque fissuring or rupture, especially at the junction of the cap and the vessel wall. Disruption of a formed plaque is a complex pathologic process that is central to the initiation of the acute coronary syndromes. Sudden total or near-total arterial occlusion frequently develops in arteries that previously appeared to have minimal stenosis. Two thirds of arteries with plaques that rupture and in which a totally occlusive thrombus subsequently develops have stenosis of 50 percent or less before plaque rupture and in 97 percent of patients,




The pathogenesis of acute coronary syndrome is shown in the above images

stenosis is initially less than 70 percent. The arterial lesions of patients with unstable angina frequently have complex, eccentric morphologic features on coronary angiography; such features have been found to represent ruptured plaque with superimposed thrombus.

**Thrombosis and Platelet Aggregation**

Exposure of subendothelial components provokes platelet adhesion and activation. Platelets then aggregate in response to exposed vessel wall collagen or local aggregates (e.g. thromboxane, adenosine diphosphate). Platelets also release substances that promote vasoconstriction and production of thrombin. In a reciprocating fashion, thrombin is a potent agonist for further platelet activation and it stabilizes thrombi by converting fibrinogen to fibrin.

Local thrombosis occurring after plaque disruption results from complex interactions among the lipid core, smoothmuscle cells, macrophages and collagen. The lipid core is the most potent substrate for platelet-rich thrombus formation and both smooth muscle and foam cells within the core correlate with the expression of tissue factor in unstable plaques. Once exposed to blood, tissue factor interacts with factor VIIa to initiate a cascade of enzymatic reactions resulting in the local generation of thrombin and deposition of fibrin. Because of the delicate equilibrium between thrombosis and endogenous thrombolysis, some acute vascular lesions resolve when fissures are repaired. As

part of the response to any type of disruption of the endothelial wall, platelets aggregate and release granular contents that further propagate platelet aggregation, vasoconstriction and thrombus formation.

Systemic factors and inflammation also contribute to alterations in the hemostatic and coagulation pathways and may play a part in the initiation of the intermittent thrombosis that is characteristic of unstable angina. The nonocclusive thrombus of unstable angina can become transiently or persistently occlusive. Depending on the duration of occlusion, the presence of collateral vessels and the area of myocardium perfused, recurrent unstable angina, NQMI or Q-wave infarction can result.

**Coronary Vasospasm**

Most patients with acute coronary syndrome have recurrent transient reduction in coronary blood supply because of vasoconstriction and thrombus formation at the site of atherosclerotic plaque rupture. These events occur because of episodic platelet aggregation and complex interactions among the vascular wall, leukocytes, platelets and atherogenic lipoproteins. Although not central to the underlying pathogenesis of the acute coronary syndromes, episodic vasospasm may contribute to vascular instability by altering preexisting coronary plaques, which causes intimal disruption and penetration of macrophages or aggregation of platelets. These processes in turn may lead to the formation of foam cells and the proliferation of smooth-muscle cells.

**Supply-demand mismatch**

Secondary disorders cause ischemia by increasing myocardial oxygen demand (e.g. thyrotoxicosis, cocaine, severe illness, physiologic stress) or by decreasing oxygen supply (e.g. hypoxemia, anemia, hypotension). Such causes must be investigated because most of these conditions are reversible. More than one of these processes may be involved. Among patients with UA/NSTEMI studied at angiography, approximately 5% have left main stenosis, 15% have three vessel CAD, 30% have two-vessel disease, 40% have single vessel disease and 10% have no critical coronary stenosis. The "culprit lesion" on angiography may show an eccentric stenosis with scalloped or overhanging edges and a narrow neck. Angioscopy may reveal "white" (platelet-rich) thrombi, as opposed to "red" thrombi, more often seen in patients with acute STEMI. Patients with UA/NSTEMI often have multiple plaques vulnerable to disruption.

**Risk assessment (Diagnosis)**

A diagnosis of unstable angina requires determination of the likelihood of CAD and assessment of the severity of presentation. The likelihood of significant CAD in patients presenting with acute chest pain syndrome is related to the physician's assessment of the patients' symptoms as angina, categorized as definite, probable, probably not or definitely not angina; evidence of prior MI or other indicators of CAD and the sex, age and number of major risk factors for atherosclerosis. The standard 12-lead electrocardiogram (ECG) provides crucial information in the diagnosis of unstable angina.

NICE recommends that as soon as the diagnosis is made; formally assess the risk of future adverse cardiovascular events using an established risk scoring system (for example, global registry of acute cardiac events based on observational study and registry database evidence). Formal risk assessment may include :

- A full clinical history (including age, previous myocardial infarction and previous percutaneous coronary intervention or coronary artery bypass grafting)
- A physical examination (including measurement of blood pressure and heart rate)
- A resting 12 lead ECG (looking particularly for dynamic or unstable patterns that indicate myocardial ischaemia)
- Blood tests (including concentrations of troponin I or troponin T, creatinine, glucose and haemoglobin).

**UNSTABLE ANGINA : RISK STRATIFICATION**

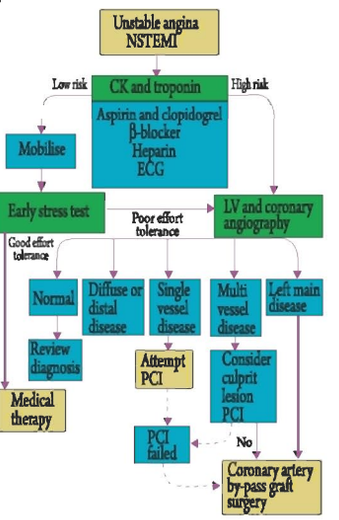
| | High risk | Low risk |
|---|---|---|
| **Clinical** | Post-infarct angina<br>Recurrent pain<br>at rest heart failure | No history of MI<br>Rapid resolution of<br>heart failure symptoms |
| **ECG** | Arrhythmia<br>ST depression<br>Transient ST elevantion<br>Persistent deep T-wave inversion | Manor or no<br>ECG changes |
| **Biochemistry** | Troponin T> 0.1 µg/l | Troponin T< 0.1 µg/l |

N.B. There is a 5-to 10-fold difference in risk between the lowest and highest risk groups.

**Current treatment modalities**

***Medical Treatment***

Patients with UA/NSTEMI should be placed at bed rest with continuous ECG monitoring for S T- segment deviation and cardiac rhythm. Ambulation is permitted if the patient shows no recurrence of ischemia (discomfort or ECG changes) and does not develop a biomarker of necrosis for 12–24 h. Medical therapy involves simultaneous anti-ischemic treatment and antithrombotic treatment.




A guide to the investigation and treatment of unstable angina and non-ST segment elevation myocardial infarction (NSTEMI).

***Nitrates***

Nitrates should first be given sublingually or by buccal spray (0.3–0.6 mg) if the patient is experiencing ischemic pain. If pain persists after three doses given 5 min apart, intravenous nitroglycerin (5–10 μg/min using nonabsorbing tubing) is recommended. The rate of the infusion may be increased by 10 μg/min every 3–5 min until symptoms are relieved or systolic arterial pressure falls to <100 mmHg. Topical or oral nitrates can be used once the pain has resolved or they may replace intravenous nitroglycerin when the patient has been pain-free for 12–24 h. The only absolute contraindications to the use of nitrates are hypotension.

***Antiplatelet treatment***

NICE recommends initial single loading dose of 300 mg aspirin as soon as possible and continue indefinitely unless contraindicated by bleeding risk or aspirin hypersensitivity. Offer a loading dose of 300 mg clopidogrel in addition to aspirin to patients with a predicted six month mortality of more than 1.5% or to patients who may undergo percutaneous coronary intervention within 24 hours of admission to hospital, unless contraindications (for example, excessive risk of bleeding) exist.

Adding an intravenous glycoprotein IIa/IIIb inhibitor (eptifibatide or tirofiban) as part of early management for patients at intermediate or higher risk (predicted six month mortality >3.0%) who are scheduled to undergo coronary angiography (and follow on percutaneous coronary intervention if indicated) within 96 hours of hospital admission is also considered though this is still an off label use of eptifibatide and tirofiban which is based on high quality systematic reviews, RCTs and cost effectiveness evidence. When determining whether a glycoprotein IIb/IIIa inhibitor should be offered, balance the potential reduction in ischaemic risk with any increased risk of bleeding.

***Antithrombotic treatment***

As with antiplatelet treatment, the choice and dose of antithrombin is carefully considered in patients who have a high risk of bleeding associated with advancing age, known bleeding complications, renal impairment and low body weight.

Based on evidence from a high quality RCT and cost effectiveness evidence, fondaparinux, an anticoagulant may be offered to patients who do not have a high bleeding risk, unless coronary angiography (and follow-on percutaneous coronary intervention if indicated) is planned within 24 hours of admission.

Unfractionated heparin, with dose adjustment guided by monitoring of clotting function, can be considered as an alternative to fondaparinux for patients with clinically important renal impairment (creatinine >265 μmol/l) or if coronary angiography (and follow-on percutaneous coronary intervention if indicated) is planned within 24 hours of admission.

Offer additional intravenous unfractionated heparin (50-100 U/kg) in the cardiac catheter laboratory to patients receiving fondaparinux who are undergoing percutaneous coronary intervention.

As an alternative to the combination of a heparin plus a glycoprotein IIb/IIIa inhibitor, bivalirudin may used for patients who are:

- At intermediate or higher risk of adverse cardiovascular events (predicted six month mortality >3%)
- Not already receiving a glycoprotein IIb/IIIa inhibitor or fondaparinux
- Scheduled to undergo coronary angiography (with follow-on percutaneous coronary intervention if indicated) within 24 hours of admission.

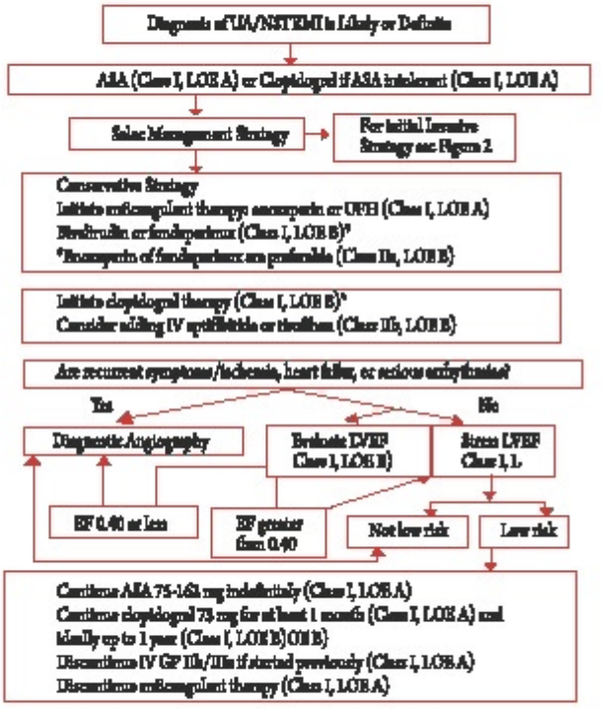
As an alternative to the combination of a heparin plus a glycoprotein IIb/IIIa inhibitor, bivalirudin can also be used for patients undergoing percutaneous coronary intervention if the patient is at intermediate or higher risk of adverse cardiovascular events and the patient is not already receiving a glycoprotein IIb or IIIa inhibitor or fondaparinux.

***Adrenergic Blockers***

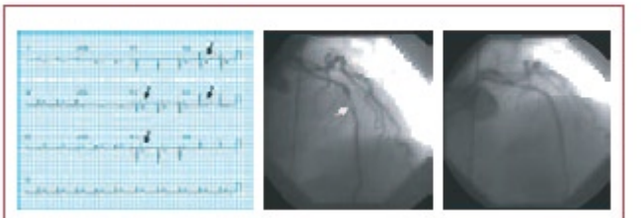
These agents are the other mainstay of anti-ischemic treatment. Intravenous beta blockade followed by oral beta blockade targeted to a heart rate of 50–60 beats/min is recommended. Heart rate slowing calcium channel blockers, e.g. verapamil or diltiazem, are recommended in patients who have persistent or recurrent symptoms after treatment with full dose nitrates and beta blockers and in patients with contraindications to beta blocker. If pain persists despite intravenous nitroglycerin and beta blockade, morphine sulfate, 1–5 mg intravenously, can be administered every 5–30 min as needed.

***HMG-CoA reductase inhibitors***

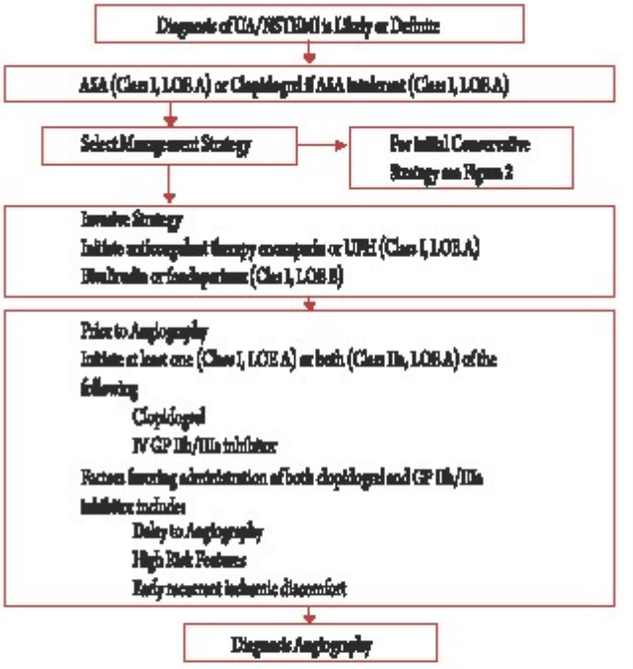
HMG coenzyme-A reductase inhibitors (statins) used to treat hypercholesterolemia and for long-term secondary prevention. Highly efficacious and very well tolerated. Multiple large, randomized, secondary prevention trials including the Heart Protection Study have demonstrated significant mortality benefit from statin therapy. Recent results from the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) TIMI trials suggest that early initiation of antilipidemic agents (statins) in patients with ACS can decrease adverse events within a relatively short term.




*Algorithm for Initial Conservative Strategy (Adapted from 2007 ACC/AHA UA/NSTEMI Guidelines).*



*Electrocardiogram of a 48 year old woman with unstable angina (left). Acute ischaemic changes seen in leads V1 to V5 (arrows). Coronary angiography revealed a severe mid-left anterior descending coronary artery stenosis (arrow left), stented (right)*




*Algorithm for Initial Invasive Strategy (Adapted from 2007 ACC/AHA UA/NSTEMI Guidelines).*

### Invasive management

Multiple clinical trials have shown the benefit of an early invasive strategy in intermediate or high-risk patients, i.e. patients with multiple clinical risk factors, ST-segment deviation and/or positive biomarkers. In this strategy, following treatment with anti-ischemic and anti-thrombotic agents, coronary arteriography is carried out within ~48 h of admission, followed by coronary revascularization (PCI or coronary artery bypass grafting). Consideration must be made taking account of coronary angiographic findings, comorbidities and the benefits and risks of each intervention.

**Class I Recommendations for Use of an Early Invasive Strategy**

Class I (level of evidence A) indications
- Recurrent angina at rest/low-level activity despite Rx
- Elevated TnT or TnI
- New ST-segment depression
- Rec. angina/ischaemia with CHF symptoms, rales, MR
- Positive stress test
- EF < 0.40
- Decreased BP
- Sustained VT
- PCI < 6 months, prior CABG

### Prognosis

After the likelihood for coronary artery disease is determined to be significant, the next step is to stratify the patient's risk for an event. The estimation of likelihood of significant coronary artery disease is critical for identifying high-risk patients who may benefit from more aggressive treatment strategy (i.e. cardiac catheterization).

The TIMI Risk Score for unstable angina/NSTEMI is currently the best validated prognostic instrument that is simple enough to use in an emergency department setting. The gradient of death, myocardial infarction or severe recurrent ischemia is somewhat proportionate to the TIMI Risk Score. The presence of any of the

following variables constitutes 1 point, with the sum constituting the patient risk score on a scale of 0-7 :

- Aged 65 years or older
- Use of aspirin in the last 7 days
- Known coronary stenosis of 50% or greater
- Elevated serum cardiac markers
- At least 3 risk factors for coronary artery disease (including diabetes mellitus, active smoker, family history of coronary artery disease, hypertension, hypercholesterolemia)
- Severe anginal symptoms (2 or more anginal events in the last 24 h)
- ST deviation on ECG

The inflection point for death or myocardial infarction starts at a TIMI Risk Score of 3. Therefore, patients with a score of 3-7 should be considered for use of intravenous glycoprotein IIb/IIIa agents, heparin (low molecular weight or unfractionated) and early cardiac catheterization.

**Conclusion**

The diagnosis of unstable angina or non-ST segment elevation myocardial infarction is based largely on the clinical presentation and demands urgent hospital admission and coronary monitoring. A clinical history and examination, 12 lead electrocardiography and measurement of troponin concentration are the essential diagnostic tools. Bed rest, aspirin, clopidogrel, heparin, antianginal drugs and opiate analgesics are the mainstay of initial treatment.

Early risk stratification will help identify high risk patients, who may require early treatment with glycoprotein IIb/IIIa inhibitors, angiography and coronary revascularisation. Those deemed suitable for percutaneous intervention should receive a glycoprotein IIb/IIIa inhibitor and stenting as appropriate. There seems to be little merit in prolonged stabilisation of patients before percutaneous intervention and an early invasive strategy is generally preferable to a conservative one except for patients at low risk of further cardiac events. This approach will shorten hospital stays, improve acute and long term outcomes and reduce the need for subsequent intervention.

Statins should be used to lower blood lipid levels. Long term treatment with aspirin, clopidogrel (especially after stenting), blockers, angiotensin converting enzyme inhibitors and antihypertensive drugs should also be considered. Antiischaemic drugs may be stopped when ischaemia provocation tests are negative.

In the longer term, aggressive modification of risk factors is warranted. Some studies have shown that lifestyle changes (weight loss/physical exercise, stop smoking) and also keeping strict control of your blood pressure, diabetes and cholesterol levels can help prevent some anginal attack.

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A drug allergy is one type of harmful or adverse drug reaction. It causes when the immune system mistakenly creates an immune response to a medication. The immune system recognizes the drug as a foreign substance and the body produces certain chemicals such as large amounts of histamine in an attempt to expel the drug from the body.

Some drug allergies are mild and the symptoms go away within a few days after stop using the medicine. But some drug allergies can be very serious. If one has an allergic reaction to a drug he/she will probably always be allergic to that drug. He/she can also be allergic to other drugs that are similar to it.

**Drugs that commonly cause an allergic reaction**

Any medicine can cause an allergic reaction. The most common drug associated with allergies is penicillin (such as nafcillin, ampicillin or amoxicillin). Other common allergy causing drugs include :

- Sulfa drugs
- Barbiturates
- Anticonvulsants
- Insulin
- Vaccines
- Iodine (found in many X-ray contrast dyes)
- Medicines for hypertension

If any one allergic to one medicine, he/she may be allergic to others like it. For example, if one is allergic to penicillin, he/she may also be allergic to similar medicines such as cephalosporins (cephalexin or cefuroxime ). People with AIDS or Lupus may be allergic to many types of medicines.

**Symptoms of Drug Allergy**

Symptoms can range from mild to life threatening and may appear within 1 to 72 hours. The most common symptoms of drug allergies are:

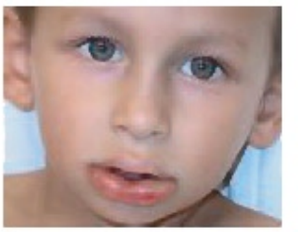
- Hives
- Rash
- Itchy skin or eyes
- Nausea, diarrhea etc.

***A more severe reaction may include :***

- Difficulty breathing
- Coughing
- Wheezing
- Runny nose
- Fever
- Shock
- Blueness of the skin
- Dizziness
- Fainting and anxiety

***Toxic epidermal necrolysis*** is a serious life threatening condition that involves blistering and peeling of the skin.

***Anaphylaxis*** is the most serious reaction. It is life threatening and will need emergency treatment.



**Diagnosis of Drug Allergies**

A doctor can diagnoses a drug allergy by carefully reviewing medical history and symptoms by asking questions about the medicines taken in the past. He or she may do a physical examination. If any doctor suspects that somebody is allergic to an antibiotic such as penicillin, he or she may do a skin test to confirm it. However, skin testing does not work for all drugs and in some cases it could be dangerous. Skin tests can diagnose allergies to :

- Penicillin, which is the most common cause of drug allergies
- Insulin
- Heterologous serum (used in the prevention or treatment of botulism, diphtheria, severe gangrene, organ transplant rejection and snake or spider bites)
- Streptokinase (used to dissolve blood clots)
- Chymopapain (used for herniated discs)

Another way to find the cause of drug allergic reaction is a medicine challenge. In a medicine challenge, a patient start by taking small doses of a medicine and slowly increase how much he/she can take to see whether he/she have an allergic reaction or not. This challenge is usually done where emergency medical help is available and under the supervision of a health professional.

**Management & Prevention of Drug Allergies**

Prevention is ideal option for drug allergy. Steps to prevent allergic drugs reactions include (1) a careful history to determine host risk factors, (2) avoidance of cross-reactive drugs, (3) use of predictive tests when available, (4)Proper and prudent prescribing of drugs (especially antibiotics) that are frequently associated with adverse reactions, (5) Use of oral drugs when possible and (6) documentation of allergic drug reaction in the patient medical record.

For some allergic drug reaction, withdrawal of the drug may be all that is required for treatment. Anaphylactic reactions require prompt emergency treatment. Glucocorticosteroids may be required for immune complex reactions, drugs induced hematologic disease, early stages of erythema multiforme major and contact sensitivities.

**Treatment in mild symptoms**

- Take cool showers or apply cool compresses.

- ❑ Wear light clothing that doesn't bother your skin.
- ❑ Take it easy, keep your activity level low.
- ❑ Stay away from strong soaps, detergents and other chemicals, which can make itching worse.

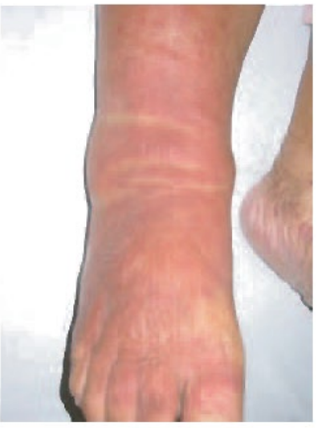
Several medicines can help to ease or relief symptoms like rash, itching etc. Using calamine lotion or taking over-the- counter antihistamines, including diphenhydramine, chlorpheniramine maleate or loratadine etc. will be helpful to relief symptom.

**Emergency treatment**

- ❑ If one have an allergic reaction that threatens life, trouble in breathing, start to develop hives or other symptoms of anaphylaxis, then he/she may need to give themself an epinephrine shot and should provide emergency medical treatment. In case of severe allergic reaction, one's first treatment may occur in an emergency room or emergency personnel may treat the person where the reaction occurs. In the absence of taking self epinephrine shot, the person may need others help to breathe. May also need to take other medicines, such as antihistamines and steroids.

**Other treatment**

Careful history taking and by using predictive tests (if available) may reveal drugs those responsible for allergic reaction for a particular person. Alternative drugs can be chosen in that cases. If it is not possible, desensitization therapy is another option to get relief from allergic reaction.



- ❑ In desensitization therapy, the patient will start to take small amounts of offending medicine that will cause allergic reaction. The patient will then gradually increase how much he/she take. This lets patient's immune system "get used to" the medicine. After this, patient may no longer have an allergic reaction. Because he/she may have a severe reaction during this therapy, it should done where emergency medical help is available and under the supervision of a health professional.

**Life style & Self care**

- ❑ If one have an allergy to a drug, the most important thing he/she can do is learn as much as possible about own potential allergic reactions and then take steps to avoid and treat potential reactions.
- ❑ It's a good idea to always wear a medical alert jewelry or bracelet that lists one's drug allergies. He/she might also carry an alert card in wallet or purse.
- ❑ Doctor may give an allergy kit that contains a shot of epinephrine and antihistamine tablets. The patient should keep that allergy kit at all times. Be sure to check the expiration dates on the medicines and replace them as needed.
- ❑ Patient should take the self epinephrine shot as soon as he/she feel a reaction starting. Then take the antihistamines.

  Patient should take the help from emergency room every time when reaction occurs even if he/she are feeling better. Symptoms can develop again even after the epinephrine shot.
- ❑ Patient should keep a list of all the medicines he/she take, including supplements and over-the-counter medicines. Share this list with your doctor. This will help him or her identify a medicine that may be allergic too.
- ❑ Before start a new medicine, he/she should ask the doctor if it may cause an allergy. This includes asking about supplements and over-the-counter medicines. One may have to take the medicine for the first time in the doctor's office.
- ❑ Do not use someone else's medicine or share yours. A medicine may appear the same but have a part that can cause a reaction.
- ❑ If one have allergies to many different medicines, be careful when start any new medicine. Taking a new medicine first time should take it at doctors office or at a hospital where one can get immediate treatment if drug reaction occurs.

**Conclusion:**

An allergic reaction may not always occur on the first exposure to a substance. The first exposure allows the body to create antibodies and memory lymphocyte cells for the antigen. However, drugs often contain many different substances, including dyes, which could cause allergic reactions. This can cause an allergic reaction on the first administration of a drug. For example, a person who developed an allergy to a red dye will be allergic to any new drug which contains that red dye. Learn as much as possible about your own potential allergic reactions and then take steps accordingly. The easiest way to prevent an allergic reaction to a drug is to avoid the drug entirely. If you have had a previous serious reaction to any drug, you should carry and know how to use an allergy kit which contains a shot of epinephrine.

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Sri Lanka's Deputy Minister of Health Mr. Lalith Dissanayake visited Square's Pharmaceuticals plant on 26th July 2011

H.E. Lyonpo Zangley Dukpa, Minister of Health, Royal Govt. of Bhutan along his entourage has visited Square Pharma's Dhaka Plant.

Scientific seminar on management of hypertension and diabetes has been organized in April 2011 at Phnom Penh, Cambodia

A group of doctors from Afghanistan has visited Square in 2011.

# Test Yourself 27

**1. All the following regarding "Postpartum Depression" is correct except:**

a. Postpartum blues almost always go away in a few days.

b. Postpartum depression does not last longer but is more intense.

c. Loss of appetite, insomnia, severe mood swings are all the signs & symptoms of postpartum depression.

d. Extreme confusion, memory loss, incoherence are the symptoms in postpartum psychosis.

**2. The following points are true for "Influenza" except:**

a. Flu viruses are classified as types A, B and C.

b. Pandemic flu refers to the flu outbreak that occurs yearly.

c. Fever, sore throat, headache are the only symptoms in flu..

d. Chest discomfort is often severe in case of flu.

**3. The below mentioned points are true for "Postpartum Depression (PPD)" except:**

a. Effective management of PPD can be done by pharmacological interventions only.

b. Interpersonal therapy (IPT) and cognitive behavioral therapy are effective non-pharmacologic treatment of PPD.

c. Antidepressants are recommended to treat the core symptoms of PPD.

d. SSRIs are considered the second line agents for the treatment of PPD.

**4. All the following points are true for "Influenza" except:**

a. Viral culture, RT-PCR, EIA can help the diagnosis of influenza..

b. Antiviral drugs are important in the management of seasonal influenza.

c. Oseltamivir are effective only for the treatment of influenza A and B infection.

d. Oseltamivir may currently be used to treat influenza in children aged one year and older.

**5. All the following are correct regarding "Unstable Angina" except:**

a. Unstable angina shows common pathoohysiological mechanisms with acute MI.

b. The standard 12 lead ECG provides crucial information in the diagnosis of unstable angina.

c. Troponin T, creatinine and glucose are the only blood tests done for the diagnosis of unstable angina.

d. Nitrates should first be given sublingually or by buccal spray if the patient experiencing ischemic pain.

**6. All the following points are true for "Drug Allergy" except:**

a. Penicillin, anticonvulsants, insulin, vaccines are common to trigger the allergic reaction.

b. Symptoms of drug allergy may appear within 1 to 48 hours.

c. Difficulties in breathing, wheezing, shock, dizziness are among the most severe reactions.

d. Antihistamines, calamine lotion can help to relief symptoms like rash and itching.

## Olmecar™

### PRESENTATION

**Olmecar™ 20** tablet: Each film coated tablet contains Olmesartan Medoxomil INN 20 mg.

**Olmecar™ 40** tablet: Each film coated tablet contains Olmesartan Medoxomil INN 40 mg.

### DESCRIPTION

Olmesartan medoxomil is a selective angiotensin II receptor antagonist (AT1subtype). Olmesartan medoxomil a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract.

### USES

For the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

### DOSAGE & ADMINISTRATION

Dosage must be individualized. The usual recommended starting dose of Olmesartan 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 of Olmesartan may be increased to 40 mg. Doses above 40 mg do not appear to have greater effect. Twice-daily dosing offers no advantage over the same total dose given once daily. 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. For patients with possible depletion of intravascular volume (e.g. patients treated with diuretics, particularly those with impaired renal function), Olmesartan should be initiated under close medical supervision and consideration should be given to use of a lower starting dose. Olmesartan may be administered with or without food.

### CONTRAINDICATION

Olmesartan is contraindicated in patients who are hypersensitive to any component of this product.

### SIDE EFFECTS

Treatment with Olmesartan was well tolerated, with an incidence of adverse events similar to placebo. The following adverse events occurred in placebocontrolled clinical trials at an incidence of more than 1% of patients treated with Olmesartan but also occurred at about the same or greater incidence in patients receiving placebo: back pain, bronchitis, creatine phosphokinase increased, diarrhea, headache, hematuria, hyperglycemia, hypertriglyceridemia, influenzalike symptoms, pharyngitis, rhinitis and sinusitis.

### USE IN PREGNANCY AND LACTATION

Pregnancy Categories: C (first trimester) and D (second and third trimesters).

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. 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.

### PAEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

### PRECAUTION

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with olmesartan medoxomil. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with olmesartan medoxomil.

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