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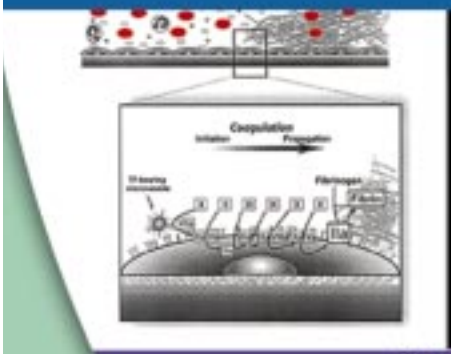
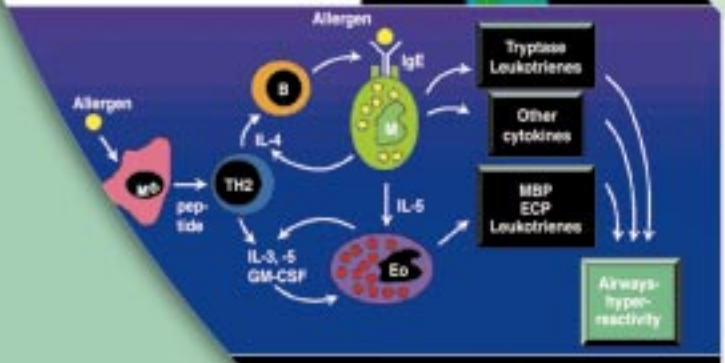
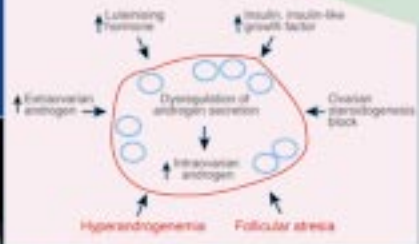
the SQUARE

healthcare bulletin







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IN THIS ISSUE:

"*the SQUARE*"

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From the Desk of Managing Editor

Dear Doctor:

We are very happy to present you the second issue of *"the SQUARE"* of 2005! We express our heartiest appreciation for your momentous feedback regarding the first issue of this year and also delighted to have many of you join our online *"e SQUARE"* community!

In this issue we published a special feature on "Polycystic Ovary Syndrome (PCOS)", one of the most common hormonal abnormalities in women of reproductive age and is a leading cause of infertility. We also bring you all the details on "Deep Venous Thrombosis (DVT)" which is more commonly seen in adults over age 60 but can occur in any age group. We also focused on "Vitiligo", the condition can be cosmetically disfiguring and affects 0.1-2% of the world's population, irrespective of gender and race. In addition, we emphasized on the essentials of "Childhood Asthma", one of the most common chronic diseases of childhood and a greater percentage of children suffer from this condition now than ever before.

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

We believe you will enjoy reading this publication and that the contents provided will prove helpful towards your goal of optimum health!

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

Omar Akramur Rab

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women and the most common cause of anovulatory infertility, affecting 5-10% of the population. Interest in PCOS has increased recently with the realization that this syndrome involves far more than the reproductive system. Initially it is called as Stein-Leventhal syndrome after its researchers in the 1930s. PCOS is now recognized to be a metabolic syndrome which may include hyperinsulinemia, hyperlipidemia, diabetes mellitus, and possibly cardiac disease, as well as the more conventionally recognized increase in androgen levels, cosmetic problems, anovulation, infertility, endometrial cancer and obesity. PCOS is generally underdiagnosed, and menstrual abnormalities, such as cycles shorter than 21 days or longer than 35 days, are often associated with the condition. Many young women with these disorders are prescribed the oral contraceptive pill, which masks the condition until they try to achieve pregnancy.

Diagnostic Criteria

The diagnostic criteria for PCOS are controversial, diagnosis is generally based on peripubertal onset of menstrual problems with clinical or biochemical hyperandrogenism.

Criteria for PCOS and related disorders :
(Criteria of US National Institute of Health)
PCOS:

- Presence of menstrual abnormalities and anovulation
- Presence of clinical and/or biochemical hyperandrogenemia
- Absence of hyperprolactinemia or thyroid disease
- Absence of late-onset congenital adrenal hyperplasia
- Absence of Cushing's syndrome

Polycystic ovaries:

- Presence of polycystic ovaries on ultrasound examination
- Absence of menstrual or cosmetic problem
- Absence of biochemical hyperandrogenemia

Idiopathic hirsutism:

- Presence of excess hair growth
- Absence of biochemical hyperandrogenemia

A recent consensus workshop held in The Netherlands during 1st May 2003 under auspicial of the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) proposed a revision of the criteria for the diagnosis of PCOS, of which 2 out of the following 3 would be needed:

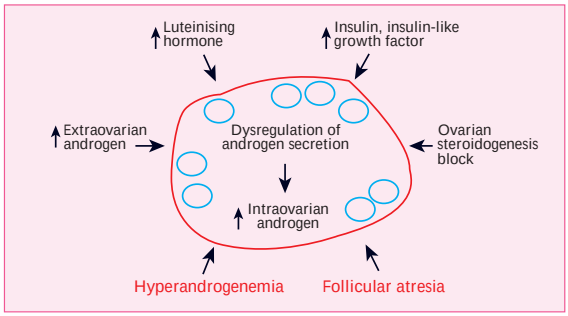
- Menstrual dysfunction – oligomenorrhea and/or anovulation
- Clinical and/or biochemical signs of hyperandrogenism, and
- Polycystic ovaries on ultrasound examination

Exclusions criteria:

- Congenital adrenal hyperplasia
- Androgen-secreting tumors
- Cushing's syndrome.

Pathogenesis

The pathogenesis of PCOS is not very clear. The primary defect may be insulin resistance leading to hyperinsulinemia. In the ovary, the cardinal feature is functional hyperandrogenism. Circulating concentrations of insulin and luteinising hormone (LH) are usually raised. The theca cells are increase in size, hyper-responsive and overproduce androgens. These androgens are converted in the ovary to estrogen. The rise in LH levels is thought to be caused by the relatively high and unchanging concentrations of estrogens that may alter the control of this hormone by the hypothalamic-pituitary axis.



Ovarian defect in PCOS

This combination of raised levels of androgens, estrogens, insulin and LH explains the classic PCOS features of hirsutism, anovulation or dysfunctional bleeding, and glucose metabolism impairment. Paradoxically, although the insulin regulatory molecules on the theca cells are responsive to insulin, those in the muscle and liver are resistant. ▶

Clinical Manifestations

PCOS is a life long condition which may affect at any age, even in the intrauterine period.

Manifestations of PCOS at different ages

Fetal life	Peripuberty	Adolescence and Adulthood	Ageing
Small baby syndrome	*Exaggerated adrenarche*	*Polycystic ovary syndrome*	*Metabolic syndrome*
❑ Intrauterine growth retardation (IUGR)	❑ Increased levels of: ◆ Adrenal androgens ◆ Insulin ❑ Functional ovarian hyperandrogenism	❑ Anovulation ❑ Hyperandrogenism ❑ Polycystic ovaries ❑ Obesity (50%)	❑ Diabetes ❑ Hypertension ❑ Dyslipidemia ❑ Increased plasminogen activator inhibitor-1
Leads to	*Leads to*	*Leads to*	*Leads to*
Long-term health effects	Precocious puberty	Reproductive disorders	Metabolic effects

Reproductive Abnormalities

Women with PCOS may present with the following abnormalities-

- ❑ Infertility (mean incidence 74%)
- ❑ Menstrual irregularity
  - ◆ Dysfunctional bleeding (DUB), 29%
  - ◆ Amenorrhea, 51%
- ❑ Hyperandrogenism, 69%, and
- ❑ Virilization, 21%.

Facial hirsutism

Axillary acanthosis nigricans

Anovulation is usually chronic in PCOS and is associated with infertility and DUB, such as oligomenorrhea or amenorrhea. The menstrual irregularity typically begins at menarche and although amenorrhea may occur, the usual presentation is oligomenorrhea. About 40% of PCOS patients are present with infertility. If pregnancy is achieved, other reproductive problems, such as miscarriage, emerge. The miscarriage rate in PCOS is about 30% of all pregnancies, which is double the rate of normal women. The exact mechanism is unknown. High levels of LH and androgens have been regarded as a cause for poor reproductive history. The unfavorable endocrine environment to which ovarian follicles are exposed could be at least partly responsible for a low percentage of pregnancies, because it affects oocyte quality and luteal phase efficiency. The prevalence of gestational diabetes (GD) in PCOS patients has been reported to be 40-46%.

PCOS and Metabolic Syndrome

Long-term health consequences: PCOS patients tend to be obese with abdominal deposition of body fat and insulin resistance. These patients also tend to have hypertension, higher levels of triglycerides, low-density lipoprotein (LDL)- cholesterol, and total cholesterol, with lower high density lipoprotein (HDL)- cholesterol. Insulin resistance is associated with an unfavorable lipid profile. Hyperinsulinemia inhibits lipolysis with a consequent increase in levels of nonesterified fatty acids (NEFAs). High levels of NEFAs led to increased triglyceride levels and reduced HDL levels. Elevated plasminogen activator inhibitor-1 (PAI-1) levels have been reported in obese women and lean PCOS patients, and a direct correlation with insulin resistance. PAI-1 is a potent inhibitor of fibrinolysis. Elevated levels of fibrinogen, an independent risk for developing CVD, has been found in PCOS patients.

Insulin resistance is recognized as a major risk factor for type 2 diabetes mellitus. Another risk factor is pancreatic β-cell dysfunction, which is also found in PCOS, presumably making PCOS patients at increased risk for type 2 diabetes mellitus. Multiple factors other than insulin resistance and β-cell dysfunction, such as obesity, and family history of type 2 diabetes, may contribute to increase diabetes risk in PCOS. ▶

The risk of endometrial disease is adversely influenced by several factors including obesity, unopposed estrogen, and infertility. All these factors are found in women with PCOS.

Investigations

History and general examination: These are needed to elicit evidence of peripubertal menstrual dysfunction and hirsutism. Gynecological examination is required only to exclude other causes of bleeding and miscarriage. Mild clitoromegaly is not uncommon, but significant enlargement raises the possibility of virilization.

Pelvic ultrasound examination: Transvaginal ultrasound is the best imaging mode. Endometrial thickness should always be assessed to exclude significant endometrial pathology.

Hormone assays: Measurement of total testosterone or testosterone adjusted for sex-hormone-binding globulin (SHBG) is helpful to show hyperandrogenemia and to rule out an androgen-secreting tumor. Diagnosis of PCOS demands exclusion of late-onset congenital adrenal hyperplasia, thyroid abnormality, hyperprolactinemia, and Cushing's syndrome.

Glucose testing: Glucose tolerance test is essential to exclude glucose intolerance. Some investigators have recommended calculating an index of insulin resistance from glucose and insulin levels (eg, the homeostasis model assessment [HOMA] or quantitative insulin sensitivity check index [QUICKI]). Random and fasting glucose levels are usually normal in women with PCOS.

Lipid status: Total and HDL cholesterol and triglyceride levels should be assessed.

Other investigations: Laparoscopy of the pelvis, computed tomography (CT scan) and magnetic resonance imaging (MRI) are never justifiable for suspected PCOS alone. Endometrial biopsy and hysteroscopy may be required to investigate unexplained vaginal bleeding.

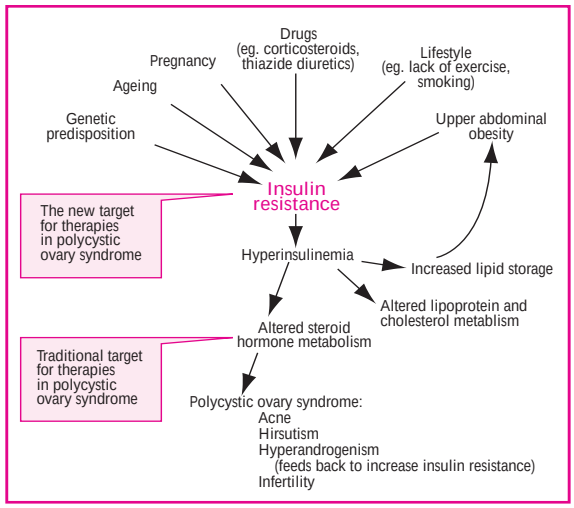
Management

Management comprises treatment of the presenting symptoms, as well as any other abnormalities discovered on investigation. The modality depends on the desire for fertility.

Hirsutism

- ❏ Oral contraceptive pill.
- ❏ Cosmetic measures: laser electrolysis, bleaching, waxing or shaving.
- ❏ Oral estrogen and cyproterone acetate (oestradiol valerate 2 mg daily and cyproterone acetate 50 mg for 14 days a month).
- ❏ Spironolactone (75-200 mg daily); or
- ❏ Other drugs, eg, antiandrogen flutamide or the antifungal agent ketoconazole.

Response times for drugs can be up to 3 months.



Pathways to insulin resistance and polycystic ovary syndrome

Menstrual dysfunction and endometrial hyperplasia

- ❏ Progestins (eg, medroxprogesterone acetate or norethisterone); or
- ❏ Oral contraceptive pill.

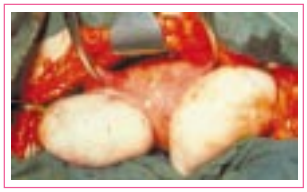
Overweight, obesity and glucose intolerance

- ❏ Lifestyle modification
- ❏ Diet
- ❏ Exercise
- ❏ Weight control
- ❏ Oral antidiabetic drugs: metformin

Infertility

- ❏ Lifestyle modification: Weight loss can lead to resumption of ovulation within few weeks. High-protein diets seem to be as effective as high-carbohydrate diets, provided that fat and total calories are comparable. While lifestyle change is difficult to maintain, women seeking pregnancy are highly ▶

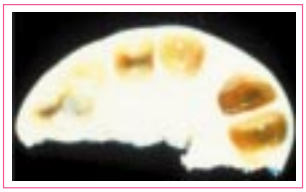
motivated, making this a first-line intervention in overweight women with PCOS. Longer-term changes in weight are more difficult to maintain.



Polycystic ovaries, showing increased size & smooth white surface reflecting thickening of the capsule

- Clomiphene citrate: This is an oral estrogen antagonist that increases the concentrations of FSH and induces follicular growth. The initial regimen is 25-50 mg per day for 5 days. Therapy can be monitored by estrogen levels, follicular ultrasound examination and luteal progesterone level (>20 nmol/L). Failure to response is associated with high body mass index and high androgen levels. Doses up to 200 mg per day can be used before failure of response is established. Tamoxifen can be used in case of withdrawal of clomiphene for side effects. Both treatments increase the risk of multiple pregnancies.
- Metformin: Use of insulin-sensitizing drug metformin at doses 500-2500 mg per day gives excellent result in increasing menstrual cyclicity and pregnancy rate. Recent studies suggest that the drug has efficacy for ovulation induction, either as a sole agent or in combination with clomiphene citrate. It has been widely used for this purpose, and no specific neonatal complications have been described. This drug also shows promising result in preventing recurrent miscarriage and to prevent gestational diabetes.

  The new insulin-sensitizer, the "glitazones"– rosiglitazone and pioglitazone – have been shown to be very effective for ovulation induction, but are not approved for PCOS. There is greater concern about the effects on the fetus of these drugs compared with metformin, and they should not be used by women trying to conceive.
- Gonadotrophin treatment: Ovulation induction with gonadotrophin such as FSH has proved successful but requires skill and experience to avoid multiple pregnancies and ovarian hyperstimulation syndrome. Low-dose recombinant FSH should be administered subcutaneously. Ovarian response should be monitored by ultrasound examination, and often by estradiol measurement. Human chorionic gonadotrophin is given when one follicle reaches 16-20 mm in size. Any more than two follicles of an appropriate size give the risk of multiple pregnancies. Multiple gonadotrophin cycles may be required to achieve pregnancy. This approach is preferable before more invasive procedures like in-vitro fertilization.



Section through polycystic ovary, showing multiple cysts with diameter <10 mm arranged around the periphery of the ovary. The stroma is increased & the ovary enlarged

- Surgery to the ovaries: Wedge resection of the ovaries has been abandoned because of concern about pelvic adhesion, subfertility, and loss of valuable ovarian tissue. Ovarian diathermy or laser drilling has been used in recent years with apparently good results.
- In-vitro fertilization: Ovulation induction by a skilled reproductive endocrinologist is preferable to in-vitro fertilization because of the risks of hyperstimulation and multiple pregnancies with the latter procedure.

Long-term management

Women with PCOS require ongoing surveillance to detect impaired glucose tolerance, hyperlipidemia, endometrial hyperplasia and consequent complications. Obese women, in particular, require regular (annual) glucose tolerance testing because of the potential for rapid progression from normal to impaired glucose tolerance and diabetes.

Some researchers have suggested prophylactic use of metformin in young teenagers and older women to avoid the problems of the metabolic syndrome. Advice about improved exercise, diet, and lifestyle modification is more effective in preventing and treating problems of glucose metabolism.

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Deep Venous Thrombosis

Swelling in one leg following childbirth was, for centuries, called "milk leg," because the swelling was believed to be caused by milk retained by mothers who did not nurse. Others thought it was due to infection or the blockage of lymph nodes. Eventually, investigations performed in the early part of the 1800s showed that the swelling was due to thrombosis in deep veins of the thigh. Today, this type of deep vein thrombosis following pregnancy, in which the painfully swollen leg appears pale in color, is called phlegmasia alba dolens.

Venous thromboembolism (VTE), manifested as either deep venous thrombosis (DVT) or pulmonary em-bolism (PE), is a common medical problem, occurring either in isolation or as a complication of other disease or procedures. DVT & PE are the major cause of morbidity and mortality. Acute DVT affects as many as 800,000 new patients per year. Untreated DVT can result in pulmonary embolism, a potentially fatal outcome. Anticoagulant therapy reduces both morbidity and mortality from venous thrombo-embolism, and early diagnosis is therefore important. Accurate diagnosis of deep venous thrombosis minimizes the risk of thromboembolic complications and averts the exposure of patients without thrombosis to the risks of anticoagulant therapy.

Etiopathogenesis

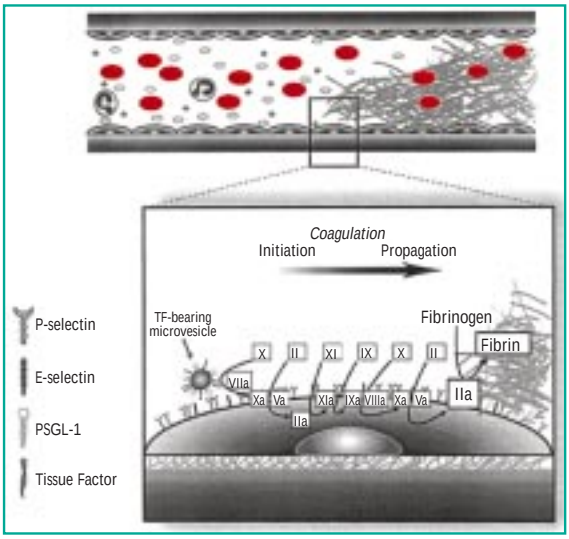
The pathophysiology of DVT is still not clearly understood. Although the cause is multifactorial, Virchow's triad (stasis, vascular injury, and hypercoagulability) defines the events that predispose a vein to the developement of thrombophlebitis. Risk factors or clinical conditions that increase the risk of DVT can be classified as either increasing the baseline propensity for thrombosis, or precipitating the thrombotic event acutely.

Potential mechanisms by which various clinical conditions may facilitate DVT

Virchow's Triad	Increased Baseline Propensity for thrombosis	Acute Insult
Hypercoagulability	*Genetic* Increased coagulants Prothrombin mutation G20210A Decreased anticoagulants Antithrombin (AT) deficiency Protein C deficiency Protein S deficiency Factor V Leiden *Acquired* Malignancy Hyperhomocysteinemia Hormone replacement therapy (HRT) / Oral contraceptive pill (OCT) Pregnancy (hormone related) Nephrotic syndrome (loss of AT) Antiphospholipid syndrome Increased levels of clotting factors	*Increased coagulants* Blood-borne tissue factors Malignancy (Trousseau's syndrome) Congestive heart failure Systemic infection Exogenous administration of clotting factors rVIIa rVIII *Acute loss of anticoagulants* Nephrotic syndrome (loss of AT) Initial warfarin therapy without heparin
Direct Vessel Injury	Endothelial injury secondary to chemotherapy Hyperhomocysteinemia Vasculitis Antiphospholipid syndrome	Intravascular catheters Trauma Surgery
Blood Stasis	Age Obesity Pregnancy (gradual immobility/stasis) Sedentarism	Hospitalization/bed ridden Pregnancy (stasis) Limb paralysis (e.g., stroke, plaster casts) Right heart failure Long-haul flights Vein compression (e.g., enlarged lymph node)

American Society of Hematology proposes a model for the formation of venous thrombosis. According to the model, endothelial stimulation or injury results from ▶

either blood stasis-induced hypoxia and/ or from direct vein wall injury (e.g., trauma). Tissue factor (TF)-bearing microvesicles from monocyte/macrophage cells attach to and fuse with stimulated endothelial cells. This interaction involves P-selectin glycoprotein ligand 1 (PSGL-1) on the microvesicle and P-selectin or E-selectin on the endothelium. Transfer of TF to the endothelial cell initiates the enzymatic cascade of coagulation reactions, leading to thrombin generation and fibrin deposition.



Model of formation of venous thrombosis

Clinical Findings

Symptoms and signs

Only 40 to 50 percent of people with DVT have obvious signs and symptoms of DVT, and the condition often goes unrecognized. When they do occur, signs and symptoms vary depending on the severity of the condition. Symptomatic patients with deep venous thrombosis may complain of:

- A dull ache
- Tightness, or
- Pain in calf or leg, especially when walking

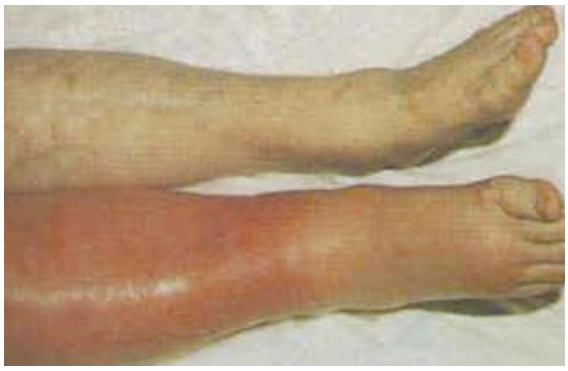
Physical examination may reveal:

- Slight edema of the involved calf
- A palpable cord
- Distension of the superficial collaterals, or
- Low-grade fever and tachycardia
- Homans' sign (pain on passive dorsiflexion of the ankle) is positive in only 50% of cases
- Iliofemoral venous thrombosis can result in cyanosis of the skin (phlegmasia cerulea dolens) or a pale, cool extremity if reflex arterial spasm is superimposed (phlegmasia alba dolens).

Diagnosis

A precise diagnosis of DVT by history and physical examination is difficult. Diagnostic studies are essential because of the difficulty in diagnosis and because of the morbidity associated with treatment.

Duplex ultrasonography: It is highly sensitive, specific, and reproducible. It is most widely used diagnostic procedure in the initial evaluation of patients suspected of having DVT. The examination includes both a B mode image and Doppler flow analysis. Each venous segment is assessed for the presence of thrombosis, indicated by venous dilation and incompressibility during light probe pressure. Doppler findings suggestive of acute thrombosis are absence of spontaneous flow, loss of flow variation with respiration, and failure to increase flow velocity with distal augmentation. The criteria for chronic venous thrombosis are less well established. The chronically occluded vein is often narrowed, and there are prominent nearby collaterals. Chronic thrombi are highly echogenic, while acute thrombi are anechoic on the B mode image. Duplex ultrasound is less accurate in detection of calf DVTs and is highly operator-dependent.



Deep venous thrombosis

Ascending contrast venography: This study is rarely used because it is invasive and exposes the patient to ionizing radiation and the risks of contrast allergy, contrast-induced nephropathy, and phlebitis. Patients in whom deep venous thrombosis is strongly suspected but ultrasound is equivocal are now being referred for ▶

gadolinium-enhanced magnetic resonance venography. This examination has a sensitivity of 100% and a specificity of 96% and may provide some information about the age of the thrombus.

D-dimer blood test: D-dimer is a marker of endogenous fibrinolysis and should therefore be detectable in patients with deep-vein thrombosis. Several studies have shown the D-dimer assay to have a high negative predictive value and D-dimer to be a sensitive but nonspecific marker of DVT.

Other tests: Many of the inherited and acquired causes of hypercoagulability can be detected by blood tests:

- Antithrombin III, protein C, protein S
- Factor V Leiden
- Prothrombin G20210A mutation
- DIC screening
- Lupus anticoagulant and anticardiolipin antibodies.

Differential diagnosis

- Localized muscle strain or contusion
- Achilles tendon rupture
- Cellulitis
- Unilateral leg edema- lymphedema, rupture of a Baker cyst, obstruction of the popliteal vein by a Baker cyst, obstruction of the iliac vein by tumor or fibrosis, or May-Thurner syndrome (external compression of left iliac vein by the right common iliac artery)
- Bilateral leg edema- heart, liver, or kidney failure, or vena caval obstruction by tumor, retroperitoneal fibrosis, or pregnancy.

Complications

- Pulmonary embolism (PE)
- Varicose veins
- Chronic venous insufficiency

Prevention

Prophylactic measures may diminish the incidence of DVT in hospitalized patients. Choice of therapy is depend on the status and individual risk factors of the patients.

Non-pharmacologic measures: DVT can be prevented by reducing venous stasis by several simple maneuvers. 15-20 degree elevation of the foot of the bed encourages venous outflow. Slight flexion of the knee is preferable. A footboard enables the patient to perform leg exercise (ankle flexion and extension) while in bed.

Sitting in a chair for prolonged time in the early postoperative period must be avoided. Early ambulance is ideal. For reduction of the risk of calf vein thrombosis, graduated compressing stockings and sequential compression devices are proven effective measures and are particularly useful in moderate-risk and high-risk patients in whom anticoagulants are contraindicated.

Anticoagulation: Low dose unfractionated heparin, 5000 units subcutaneously twice daily, and low molecular weight heparin (LMWH) e.g., enoxaparin, 30 mg subcutaneously twice daily, have both been shown to reduce the incidence of postoperative deep vein thrombosis and pulmonary embolism. LMWH appears to be more effective in the orthopedic surgery patients and is associated also with a lower risk of bleeding complications. Use of heparin products are contraindicated in patients with recent craniotomy, intracranial bleeding, or severe gastrointestinal bleeding. Either medication must be withheld 12 hours prior to placement or removal of an epidural catheter to avoid epidural hematoma. Platelet count should be monitored for early recognition of heparin-induced thrombocytop-enia, which occurs with peak incidence at 5-10 days of treatment.

Warfarin is seldom used for perioperative DVT prophylaxis but may be indicated for long-term management of minimally ambulatory patients. Lifetime anticoagulation with low-dose warfarin or prophylactic vena caval filter placement is considered in patients with hypercoagulable state or paralysis.

Treatment

Deep veinous thrombosis must be treated promptly. Treatment usually requires hospitalization, primarily to facilitate monitoring of medications. Because DVT occurs in post-surgical patients, however, the person might already be in the hospital when DVT is diagnosed.

Bed rest: Individuals with DVT usually require bed rest until symptoms are relieved. The leg should be elevated to a position above the heart to reduce swelling (the foot of the bed is elevated about six inches to achieve this). Moist heat may be applied to the affected region to relieve pain.

Compression stockings: compression stockings (also called TED or thrombo-embolic deterrent stockings) are recommended for the patients who have DVT to reduce symptoms. Compression stockings improve circulation by ▶

providing a graduated pressure on the leg to help return the venous blood to the heart.

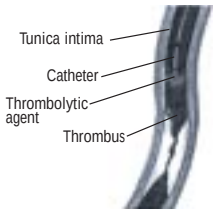
Anticoagulants: The standard treatment of deep venous thrombosis is systemic anticoagulation with heparin (initial bolus 100 units/kg followed by 10units/kg/h, dosed to a goal partial thromboplastin time of 1.5-2 times normal). This reduces the risk of pulmonary embolism and decrease the rate of thrombophlebitis recurrence by 80%. Systemic anticoagulation does not directly lyse thrombi but stops propagation and allows natural fibrinolysis to occur.

Warfarin is started after therapeutic heparinization. The two therapies should overlap to diminish the possibility of a hypercoagulable state, which can occur during the first few days of warfarin therapy (because warfarin inhibits synthesis of the natural anticoagulant proteins C and S). The recommended treatment for the first episode of uncomplicated DVT is 3-6 months of warfarin. After a second episode, warfarin is continued indefinitely. The risk of recurrent DVT is increased markedly in the presence of factor V Leiden mutations, homozygous activated protein C resistance, antiphospholipid antibody, and deficiencies of antithrombin III and protein C or protein S. Lifelong anticoagulation is recommended for these conditions.

Recently, enoxaparin at therapeutic dose (1 mg/kg subcutaneously twice daily) is safe and effective alternate for the treatment of DVT. The drug does not require monitoring of its anticoagulant effect because of its predictable dose-response relationship, so it has been promoted for use in outpatient treatment. Unfractionated heparin inhibits thrombin by complexing thrombin and antithrombin III. The enoxaparin molecule is too small to inhibit thrombin in this way. It inhibits factor Xa activity, which accounts for its lower risk of bleeding complications and thrombocytopenia. It has also demonstrated less protein C and S inhibition, less complement activation, and a lower risk of osteoporosis.

Current research efforts are directed toward innovation of an oral thrombin inhibitor. This is expected to have a more favorable dose-response curve and side-effect profile than warfarin.

Many studies have evaluated the efficacy of fibrinolytic agents in the treatment of acute DVT. Risk of bleeding complication is higher with fibinolytic agents and does not appear to be reduced by selective catheterization for local application. To get effective result, alteplase (a tissue plasminogen activator produced by recombinant DNA technology) should be instituted within after clot formation, before extensive fibrin cross-linking can occur. One possible application of alteplase is acute iliofemoral venous thrombosis complicated by massive extremity edema and cyanosis.



Catheter-directed thrombolysis

Catheter-directed thrombolysis: A thrombolytic agent is placed directly into the thrombus through a catheter to dissolve the thrombus.

Balloon angioplasty: Balloon angioplasty is used to widen the vein after the blood clot has been dissolved.

Stent: A stent may be inserted into a vein to keep the vein open if it tends to collapse. Once it is in the proper location, the stent is expanded.

Surgery: If an embolus develops, surgery may be necessary to prevent the spread of the clot to the lung. Surgery, however, is performed only as a last resort. Surgery for complications resulting from DVT involves the insertion of a filter into the inferior vena cava trap any blood clots headed toward the lungs. The procedure is called vena cava interruption.

The most severe cases of DVT may require thrombectomy. The patient is given anticoagulant therapy with heparin during the surgery, and warfarin for a period of at least six weeks to three months following the operation.

Prognosis

Prognosis is good in most cases, if DVT is diagnosed early and treated accurately. Mortality is related to pulmonary embolism, which occurs in 60% of cases with inadequately treated proximal lower extremity thrombosis.

Reference:

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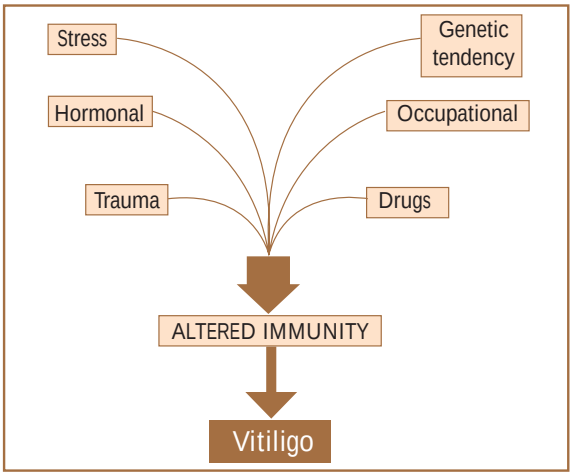
the SQUARE

Vitiligo

Vitiligo is more commonly known as leukoderma, which is a pigmentation disorder in which melanocytes in the skin, the mucous membranes, and the retina are destroyed. As a result, white patches of skin appear on different parts of the body. Lesions are often symmetrical and frequently involve the face, hands and genitalia. The hair can also depigmented. Trauma may induce new lesions. Basically, Vitiligo can hardly be called as a disease but a skin-disorder that has more social than medical significance, especially amongst the dark skinned people. Spontaneous repigmentation can occur and often starts around hair follicles giving a speckled appearance. However, repigmentation is rare if a lesion has persisted for more than 1 year or if the hair is depigmented. The psychological consequences of vitiligo can be devastated especially in Asian or black African people.

Epidemiology and Etiology

The vitiligo sufferers are observed all over the world, including the white skin communities. About 1 to 2 percent of the world's population, or 40 to 50 million people, have vitiligo. Ninety-five percent of cases vitiligo



develop before their 40th birthday. However, epidemiologically most cases are recorded in India (8.8%) and Mexico. Males and females are affected equally, inclusive of children age group. It may begin at any age. Childhood vitiligo is not uncommon.

Vitiligo seems to be more common in people with certain autoimmune diseases. These are hyperthyroidism, hypothyroidism, diabetes, adrenocortical insufficiency, alopecia areata, and pernicious anemia. The reason for the association between vitiligo and those autoimmune disorders is still unknown. However, most people with vitiligo have no other autoimmune disease.

The familial incidence is almost 20 to 30%. Vitiligo in identical twins has been reported.

Some people with vitiligo have reported that a single event such as a severe sunburn or an episode of emotional distress seems to have triggered their vitiligo. Events of this nature, however, have not been scientifically proven to cause vitiligo and may simply be coincidences.

There are a number of inherited disorders associated with vitiligo. They include: albinism of the ocular type, autoimmune polyendocrinopathy syndrome, congenital deafness with vitiligo and achalasia, dyschromatosis symmetrica hereditaria, ermine phenotype, familial histiocyctic reticulosis, kabuki syndrome, Letterer-Siwe disease, progressive hemifacial atrophy, progressive vitiligo with mental retardation and urethral duplication, Schmidt syndrome, and the syndrome of spastic paraparesis, vitiligo, premature graying and characteristic facies.

The abundance of genetic diseases associated with vitiligo clearly reflects the fact that there are a number of genes, which normally govern the development, and well being of the melanocyte. The precipitating factors have been identified as due to pressure of tight clothes (such as on the waist) or certain occupational hazards such as wearing certain rubber hand gloves. Long term intake of certain drugs is found to produce this pigment disorder. In many cases, especially in children, often have no clue why one develops vitiligo. However like many disease conditions, the exact causation yet remains a mystery!

Pathogenesis

The cause of vitiligo is not fully known, three principal theories have been presented about the mechanism of destruction of melanocytes in vitiligo. *The autoimmune theory* holds that selected melanocytes are destroyed by certain lymphocytes that have somehow been activated internally. *The neurogenic hypothesis* is based on an interaction of the melanocytes and the nerve cells. *The self-destruct hypothesis* suggests that melanocytes are destroyed by toxic substances formed as part of normal melanin biosynthesis. While the immediate mechanism ▶

for the evolving white macules involves progressive destruction of selected melanocytes by cytotoxic T cells, other genetically determined cytobiologic changes and cytokines must be involved. Because of differences in the extent and course of segmental and generalized vitiligo, the pathogenesis of these two types must be somewhat different.

History

Characterizations of the onset of vitiligo suggest that there are both predisposing (genetic) and precipitating (environmental) factors. Important factors in a patient's medical history include:

- Vitiligo in the family
- Rash
- Sunburn, or other skin trauma at the site of vitiligo 2 to 3 months before depigmentation started
- Stress or physical illness
- Premature graying of the hair (before age 35).

People who develop vitiligo usually first notice white patches on their skin. These patches are more common in sun exposed areas, including hands, feet, arms, face and lips. Other common areas for white patches to appear are the armpits and groin and around the mouth, eyes, nostrils, navel, and genitals. It has a tendency to start as a single spot and gradually grow in size and number. The spread of the disorder is usually slow and progressive. Symmetrical appearance on both the sides of the body is common.

The patches of depigmentation are sharply defined and, in Caucasians, may be surrounded by light brown 'café au lait' hyperpigmentation. Some spotty perifollicular pigment may be seen within the depigmented patches and is sometimes the first sign of repigmentation. Sensation in the depigmented patches is normal. The course is unpredictable but most patches remain static or enlarge; a few repigment spontaneously.

In addition to white patches on the skin, people with vitiligo may have premature graying of the scalp hair, eyelashes, eyebrows, and beard. People with dark skin may notice a loss of color inside their mouths.

Physical Examination

Skin Lesions

Type : Macules; 5 mm to 5 cm or more in diameter.

Color : Chalk white. Newly developed macules may be off-white in color; this represents a transitional phase. The disease progresses by gradual enlargement of the old macules or by development of new ones. Pigmentation around a hair follicle in a white macule may represent residual pigmentation or return of pigmentation. Confetti-sized hypomelanotic macules also may be observed. Inflammatory vitiligo has an elevated erythematous margin and may be pruritic; this appears to have no special significance.

Shape : convex margins with round, oval, or elongated. Linear or artifactual macules represent the isomorphic or "Koebner" phenomenon.

Distribution : Depigmentation occurs in three general patterns. The focal type is characterized by one or several macules in a single site; this may be an early evolutionary stage of one of the other types in some cases. The segmental type is characterized by one or several macules in one band on one side of the body; this type is associated rarely with distant vitiligo macules or with further evolution of the disease. The most common type is generalized vitiligo, characterized by widespread distribution of depigmented macules, often in a remarkably symmetric array. Typical macules occur around the eyes and mouth and on digits, elbows, and knees, as well as on the low back and in genital areas. The "lip-tip" pattern involves the skin around the mouth as well as on distal fingers and toes; lips, nipples, and genitalia (tip of the penis) may be involved. Extensive generalized vitiligo may leave only a few normally pigmented areas of skin ; this is referred to as vitiligo universalis.

Vitiligo-affecting different areas of face and throat

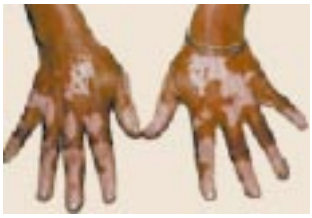
Associated Cutaneous Findings

At times, vitiligo may associate with one or more of the following conditions:

- Alopecia areata
- Premature graying of the hair
- Lichen planus
- Psoriasis
- Halo nevus
- Ichthyosis ▶

There is no increased risk for malignancy in the white skin. Skin cancers (all types) appear to be rare. In older patients, photoaging may occur in vitiligo macules with long exposures to sunlight.

General Examination:
Vitiligo is not uncommonly associated with thyroid disease (up to 30% of all vitiligo cases, and especially in women), diabetes mellitus (probably less than 5%), pernicious anemia (uncommon but increased risk), Addison's disease (uncommon), and multiple endocrinopathy syndrome (rare). Ophthalmologic examination may reveal evidence of healed chorioretinitis or iritis (probably less than 10% of all cases). Vision is unaffected. Hearing is normal.



Vitiligo-affecting hands

Differential diagnosis

- Lupus erythematosus
- Pityriasis alba
- Piebaldism
- Pityriasis versicolor alba
- Chemical leukoderma (history of exposure to certain phenolic germicides, confetti macules). This is a difficult differential diagnosis
- Leprosy (endemic areas, off-white color, anesthetic macules)
- Nevus depigmentosus
- Nevus anemicus
- Tuberous sclerosis
- Leukoderma associated with melanoma may be true vitiligo (may repigment spontaneously, usually a history of psoriasis or eczema in the same macular area), not so sharply defined.

Laboratory and special examination
Diagnosis usually can be established on clinical grounds alone; however, in certain difficult cases, a skin biopsy may be required.

Wood's lamp examination : Wood's lamp examination is required to evaluate macules, particularly in lighter skin types, and to identify macules in sun-protected areas in all but the darkest skin types.

Dermatopathology : Established vitiligo macules show normal skin except for an absence of melanocytes. There may be melanocytes at the margins (normal numbers of melanocytes that appear relatively inactive or reduced numbers that are very activated) and a mild lymphocytic response. These changes are not diagnostic for vitiligo, however only consistent with it.

Electron microscopy : Electron microscopy has demonstrated other changes in skin affected by vitiligo; these include changes in keratinocytes: spongiosis, exocytosis, basilar vacuopathy, and necrosis. Extracellular granules and lymphocytes have been seen in the epidermis.

Laboratory studies : T_4, TSH (radioimmunoassay), fasting blood glucose, complete blood count with indices (Pernicious anemia), ACTH stimulation test (Addison's disease) if suspected.

Management
Therapy of vitiligo is long, tedious and also very unsatisfactory, and the patient must be strongly motivated. Treatment has advanced significantly recently, although older therapies still retain an important place in the management of this therapeutically challenging disease.

If less than 20% of the skin is involved (most cases), topical methoxasalen, 0.1% in ethanol and propylene glycol or in Acid Mantle cream or Unibase, is used, with cautious exposure to long-wavelength ultraviolet light (UVA), followed by thorough washing and sun avoidance.

With 20-25% involvement, oral PUVA [Psoralen (P) and long-ware ultraviolet radiation (UVA)] is best. Severe phototoxic response (sunburn) may occur with topical or oral psoralens plus UVA. The face and upper chest respond best, and the fingertips and the genital areas do not respond to this treatment. Newer techniques of using epidermal autografts and cultured epidermis combined with PUVA therapy give hope for surgical correction of vitiligo.

Potent topical corticosteroids have been advocated for treatment of vitiligo, with daily use for 10 days followed by 10 days of rest, then repetition. Steroids may initially help for a very short time, however they have often dangerous and longer lasting side effects such thinning of the skin, dilated blood vessels, bruising, skin colour changes and hair loss. Vitiligo often flares up much worse after discontinuing steroids. Long term use of Cortisone ▶

can cause liver and kidney disease and worsen psoriasis.

Narrow Band Ultraviolet B (NB-UVB) is a useful and well-tolerated treatment option for patients with moderate to severe vitiligo. NB-UVB, a light source that emits a very narrow spectrum of UVB, is the portion of sunlight that causes sunburn. The application of Narrow Band UVB by itself can cause regimentation to begin in many patients. The patient applies no drugs either topically or orally. For this treatment patient needs simply expose to Narrow Band UVB rays for a relatively short time on a periodic basis either daily in some cases or 2-4 times a week. Covering areas unaffected by Vitiligo with opaque clothing or sunscreens will reduce the exposure to neighboring areas.

NB-UVB has an excellent safety profile for use in children. While NB-UVB therapy has been used in Europe since the mid-1980s, there has not been any evidence that it causes an increase in skin cancer.

Tacrolimus, the first in a new class of drugs called topical immunomodulators (TIMs) shows promise as an innovative treatment option for the patient with vitiligo. Different new study showed the success with tacrolimus in restoring pigment to affected areas. Efficacy and safety of the tacrolimus ointment in case of adult and children as a treatment for vitiligo has also been illustrated in different study. Tacrolimus ointment 0.1% is almost as effective as clobetasol propionate 0.05% in inducing repigmentation. A major advantage of tacrolimus is that it is well tolerated when used for extended periods.

Pseudocatalase cream plus calcium used as a substitution for low catalase levels in the treatment of vitiligo. Repigmentation with pseudocatalase cream PC-KUS can be achieved in all skin colors and is independent of the percentage of depigmented skin and the duration of the disease: First signs of repigmentation can be observed after 3-4 months. This treatment modality can also successfully repigment lips, ears and genitals. However, the response on fingers and feet is disappointing. The removal of high levels of epidermal H_2O_2 with Narrowband UVB activated pseudocatalase – PC-KUS coincides with – stabilization of the depigmentation process followed by repigmentation. The treatment has no side effects providing the liver function of the affected individual is normal. A significant faster initiation of repigmentation can be induced with the combination of climatotherapy together with pseudocatalase PC-KUS over a period of 21 days. First repigmentation occurs between the day 14-20. This fast repigmentation lasts for an additional 4 months when continued with daily treatment using Narrowband UVB activated pseudocatalase PC-KUS.

Sunblocks should be used to prevent burning. Camouflage cosmetics may also be helpful, particularly in those with dark skin. There is no clinical evidence that exists anywhere that proves vitamins, homeopathic or a special diet can improve, treat or cure vitiligo.

Course and Prognosis

Vitiligo is a chronic disease. The course is highly variable, but rapid onset followed by a period of stability or slow progression is most characteristic. Up to 30% of patients may report some spontaneous repigmentation in a few areas particularly areas that are exposed to the Sun. The absence of whiteness of the hairs in the area of vitiligo is a good prognostic feature. Rarely is this satisfactory to the patient. Rapidly progressive or “galloping” vitiligo may quickly lead to extensive depigmentation. Segmental vitiligo is a special subset that usually develops precipitously in one unilateral region, usually does not extend beyond that initial one-sided region, and once present is very stable. The treatment of vitiligo-associated disease (i.e. thyroid disease) appears to have no impact on the course of vitiligo.

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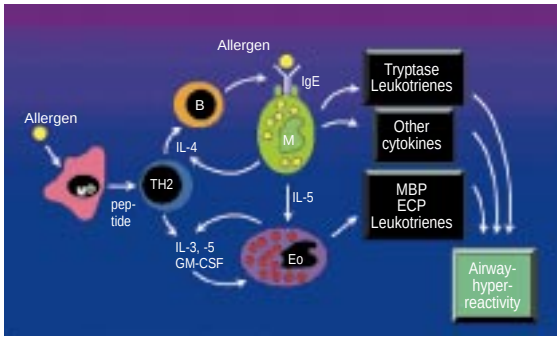
Asthma is a significant and global health-care concern affecting an estimated 8% of the adult population and possibly up to 20% of children. Asthma is a chronic inflammatory disorder of the airways characterized by hyperresponsiveness, reversible airflow limitation, and respiratory symptoms. It is a common morbidity in children. It has a potential interference with society in terms of morbidity, quality of life (physical activity, education, socialization, and self-esteem) and health care costs. The prevalence of asthma has increased over the last 3 decades, and the trends in the incidence of asthma also appear to be rising.



Development of hyperreactivity
source, Drazen et al,: J. Exp. Med. 183, 1 (1996)

Risk Factors

Provocative factors for asthma exacerbations have been well documented by epidemiologic studies, ranging from familial, allergenic, and environmental, to socioeconomic and psychological factors. The average annual incidence of physician diagnosed asthma ranged from 0.6 to 29.5 per 1000 persons. The highest estimate defined asthma as "2 episodes of cough or wheeze lasting >1-2 weeks and nocturnal symptoms or medication use".

Host factors

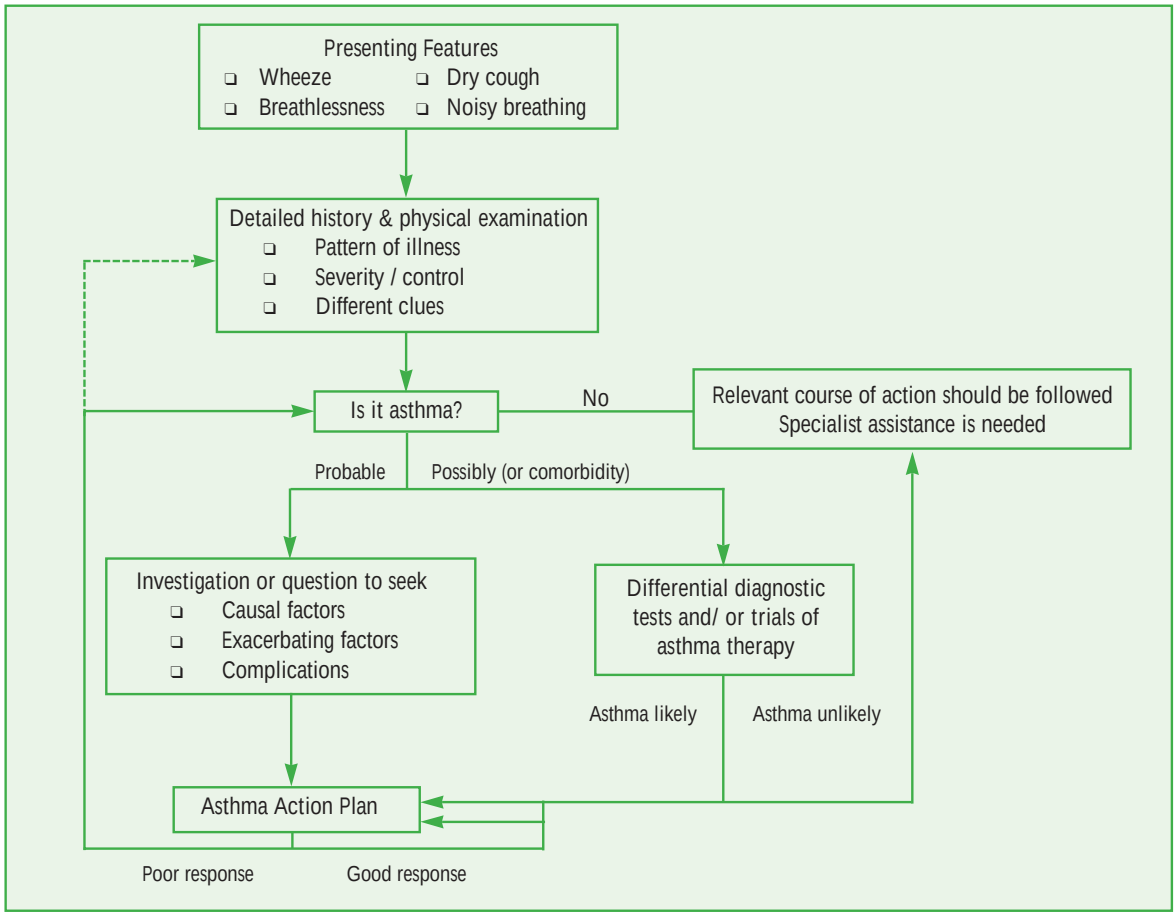
- Age: The incidence of physician-diagnosed asthma tends to increase from the 1st year of life through adolescence, and then decrease into adulthood.
- Sex: In general, studies of children found males to be at risk, whereas studies of adolescents or adults found females to be at risk.
- History of atopy and parental asthma: Personal atopy or a familial history of asthma is consistent predictors of incident asthma.
- Airway hyperresponsiveness: The risk of either developing recurrent wheezing or asthma is increased among subjects with reactive airways.

Environmental factors

- Low birth weight: Low birth weight (<2500 g) as a risk factor for incident asthma for children <11 years of age.
- Medical factors: Childhood infections, migraine headache, recurrent abdominal pain, chronic bronchitis increase the risk of incident asthma.
- Social factor: Increase exposure to other children, either playground or daycare attendance or having more siblings decreases the risk of developing asthma.
- Lifestyle factors: Smoking increases the risk of developing asthma. A positive association between higher BMI and incident asthma among children and adults has been reported.
- Indoor exposure: Indoor factors related to incident asthma include passive exposure to ETS (environmental tobacco smoke), exposure to furred pets, or other allergens, and exposure to dampness. Some studies reported that the proportion of children with incident asthma was lower among those who were exposed to furred pets during 1st year of life. A significant association between exposure to elevated cockroach allergen levels and incident asthma was reported.
- Outdoor exposure: A significant association between outdoor pollutants (i.e. ozone, particulate matter, and nitrogen dioxide) and incident asthma was found.
- Occupational exposure: Working in an environment with dust, fumes or smoke resulted in a higher risk of asthma.

Diagnosis of Asthma in Children

A definitive diagnosis of asthma can be difficult to obtain in young children. It is not often possible to measure airway function in order to confirm the presence of variable airway obstruction. Asthma should be suspected in any child with wheezing, ideally heard by a health professional on auscultation, and distinguish from upper airway noises. In schoolchildren, bronchodilator responsiveness, PEF (peak expiratory flow) variability or test of bronchial hyperractivity may be used to confirm the diagnosis. ▶



Diagnosis of asthma in children

Allergy tests are helpful in seeking causal factors, and in making a general diagnosis of atopy. The presence of allergy is not essential to the diagnosis of asthma, but its absence in a school child with symptoms suggestive of asthma should prompt consideration of alternative diagnosis.

Indications for Further Investigations in Children

- Diagnosis unclear or in doubt
- Symptoms present from birth or perinatal lung problem
- Excessive vomiting or posseting
- Severe upper respiratory tract infection
- Persistent wet cough
- Family history of unusual chest disease
- Failure to thrive
- Unexpected clinical findings e.g., focal signs in the chest, abnormal voice or cry, dysphagia, inspiratory stridor
- Failure to respond to conventional treatment (particularly corticosteroids > 400 mcg/day)
- Frequent use of steroid tablets
- Parental anxiety or need for reassurance.

Base of the Diagnosis of Asthma in Children

- The presence of key features and careful consideration of alternative diagnoses
- Assessment of the response to trials of treatment, and ongoing assessment
- Repeated reassessment of the child, questioning the diagnosis if management is ineffective. ▶

Management

Non-pharmacological management

Primary prophylaxis: Primary prophylaxis is employed before there is any evidence of disease in an attempt to prevent its onset.

- Allergen avoidance: There is a strong correlation between allergic sensitization to common aeroallergens and the subsequent development of asthma. No recommendations of prenatal or postnatal allergen avoidance can be made in relation to primary prevention of asthma.
- Breastfeeding: Breastfeeding should be encouraged and its benefits include a protective effect in relation to early life wheezing.
- Microbial exposure: The "hygiene hypothesis" suggests that early exposure to microbial products will switch off allergic responses preventing allergic disease like asthma.
- Immunotherapy and primary prevention: Preliminary results from an outgoing parallel group study using contemporaneous untreated children as the control group for pollen immunotherapy in children with allergic rhinitis suggest a lower rate of onset of asthma in the treated group.
- Avoidance pollutants: Parents and parents-to-be who smoke should be advised of the many adverse effects of smoking on their children, including increased wheezing in infancy.

Secondary prophylaxis: Interventions made after the onset of disease to reduce its impact.

Alternative diagnoses in wheezy children

Clinical clue	Possible diagnosis
Perinatal and family history	
Symptoms present from birth or perinatal lung problem	Cystic fibrosis; chronic lung disease; ciliary dyskinesia; developmental anomaly.
Family history of unusual chest disease	Cystic fibrosis; developmental anomaly; neuromuscular disorder.
Severe upper respiratory tract disease	Defect of host defense.
Symptoms and signs	
Persistent wet cough	Cystic fibrosis; recurrent aspiration; host defense disorder.
Excessive vomiting or posseting	Reflux (± aspiration)
Dysphagia	Swallowing problems (±aspiration)
Abnormal voice or cry	Laryngeal problem
Focal signs in the chest	Developmental disease; postviral syndrome; bronchiectasis; tuberculosis
Inspiratory stridor as well as wheeze	Central airway or laryngeal disorder
Failure to thrive	Cystic fibrosis; host defense defect; gastro-esophageal reflux
Investigations	
Focal or persistent radiological changes	Developmental disorder; postinfective disorder; recurrent aspiration; inhaled foreign body; bronchiectasis; tuberculosis

- Allergen avoidance: Allergen avoidance measures are helpful in reducing the severity of existing disease. Reducing allergen exposures also reduce the risk of morbidity and mortality.
- House dust mite control measures: The followings are recommended to keep the house free from mite:
  - Complete barrier bed-covering systems
  - Removal of carpets
  - Removal of soft toys from bed
  - High temperature washing of bed linen
  - Acaricides to soft furnishing
  - Dehumidification.

Environmental factors

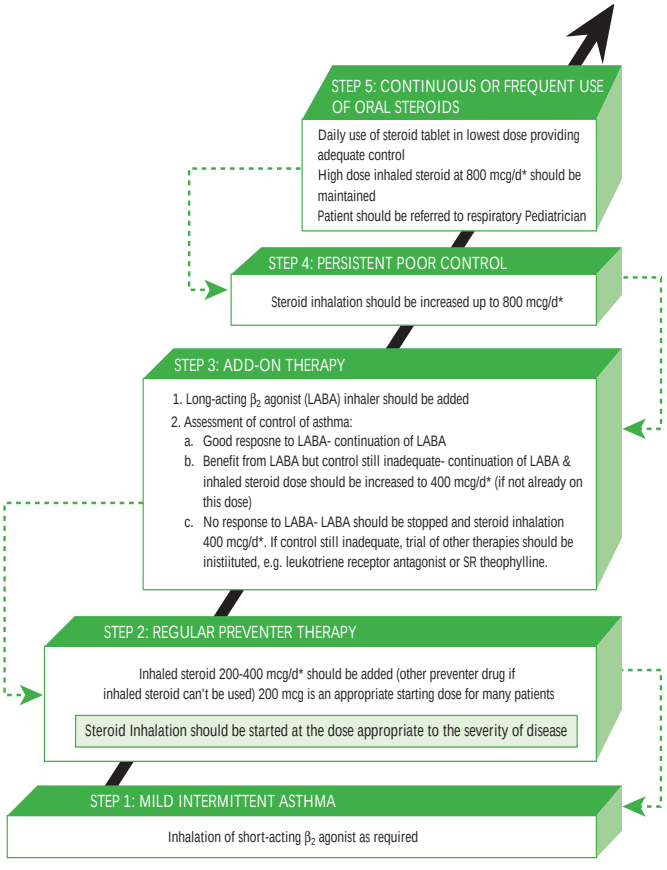
- Smoking: There is a causal relationship between parental smoking and lower respiratory illness in children up to three years of age. Infants whose mothers smoke are four times more likely to develop wheezing illnesses in the first year of life. Smoking cessation must be encouraged as it is good for general health and may reduce asthma severity. ▶

- Air pollution: Changing from high particulate sulfur dioxide (coal burning) environment to a low sulfur dioxide/high diesel particulate environment increases the incidence of asthma and atopy.

Weight reduction : Weight reduction is recommended in obese children with asthma, to improve asthma control.

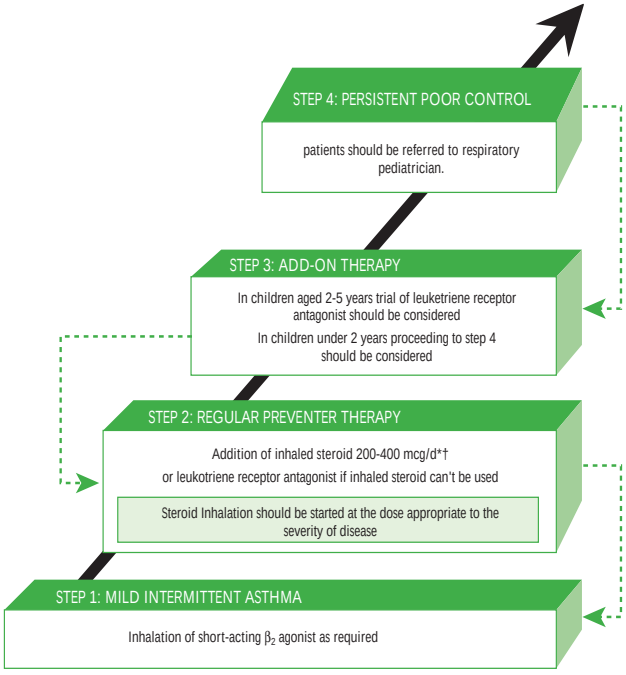
Pharmacological Management

A stepwise approach aims to abolish symptoms as soon as possible and to optimize peak flow by starting treatment at the level most likely to achieve this. Patients should start treatment at the step most appropriate to the initial severity of their asthma.



Summary of stepwise management in children aged 5-12 years

The aim is to achieve early control and to maintain control by stepping up treatment as necessary and stepping down when control is good.



Summary of stepwise management in children less than 5 years

Prognosis of Childhood Asthma

Therapeutic decisions, particularly the introduction of prophylactic treatments may be influenced by the presence of persistent symptoms, pathophysiology and the natural history of the disease. If all the factors associated with resolution and persistence of asthma presenting in childhood were not taken into account and every child presenting with wheeze was treated prophylactically, half of all children would be treated.

References:

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Product Profile- Comet® & Comet XR®

Comet® (metformin hydrochloride tablets)

Comet XR® (metformin hydrochloride extended release tablets)

Composition

Comet® 500 : Each film coated tablet contains metformin hydrochloride BP 500 mg.

Comet® 850 : Each film coated tablet contains metformin hydrochloride BP 850 mg.

Comet XR® 500 : Each extended release tablet contains metformin hydrochloride BP 500 mg.

Pharmacology

Metformin is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia.

Indications and Usage

Comet® and Comet XR® tablets are oral antihyperglycemic drugs used in the management of type 2 diabetes.

Comet® 500 mg and 850 mg tablets and Comet XR® 500 tablets, as monotherapy, are indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes or may be used concomitantly with a sulfonylurea or insulin.

Dosage and Administration

Dosage of Comet® or Comet XR® 500 must be individualized on the basis of both effectiveness and tolerance. The maximum recommended daily dose of Comet® in adults is 2550 mg and 2000 mg in pediatric patients (10-16 years of age); the maximum recommended daily dose of Comet XR® in adults (≥17 years) is 2000 mg.

Comet® should be given in divided doses with meals while Comet XR® 500 should generally be given once daily with the evening meal. Comet® or Comet XR® 500 should be started at a low dose, with gradual dose escalation, both to reduce GI side effects and to permit identification of the minimum required dose. During treatment initiation and dose titration, fasting plasma glucose should be monitored. Thereafter, HbA_{1C} should be measured at intervals of approximately three months.

Short-term administration of Comet® or Comet XR® 500 may be sufficient during periods of transient loss of control in patients usually well-controlled on diet alone.

Precaution

Pregnant mothers : Pregnancy Category B. Metformin should not be used during pregnancy unless clearly needed.

Nursing mothers: May cause hypoglycemia in nursing infants.

Pediatric use: The safety and effectiveness of metformin immediate release tablets for the treatment of type 2 diabetes have been established in pediatric patients ages 10 to 16 years. Safety and effectiveness of metformin extended release tablets in pediatric patients have not been established.

Geriatric use: The drug should only be used in patients with normal renal function.

Contraindications

Contraindicated in patient with known hypersensitivity to metformin, patients with renal impairment, CCF, acute or chronic metabolic acidosis including diabetic ketoacidosis.

The drug should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials.

Side Effects

Diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, headache, etc.

Warnings

The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases/1000 patient-years).

Drug Interaction

Furosemide: In single-dose, furosemide increases the metformin plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in renal clearance.

Nifedipine: Nifedipine appears to enhance the absorption of metformin.

Others: Certain drugs tend to produce hyperglycemia. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.

Storage Condition

The medicine should be preserved in a cool and dry place, protected from light and moisture.

How Supplied

Comet® 500 : Box containing 10 x 10 Comet® 500 tablets in blister pack.

Comet® 850 : Box containing 5 x 10 Comet® 850 tablets in blister pack.

Comet XR® 500: Box containing 5 x 10 Comet XR® 500 tablets in blister pack.

Correct answers of the 'Test Yourself - 18'

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

The following are the 10 winners of the "Test Yourself -18"; they have been selected through lottery.

Congratulations from "the SQUARE" Editorial Board

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

Test Yourself – 19

1. All the points mentioned below are correct for "Vitiligo" except:
   a. Lesions are often asymmetrical and frequently involve face, hand and genitals.
   b. Epidemiologically most cases are recorded in India & Mexico.
   c. There is no familial incidence of Vitiligo.
   d. Tacrolimus shows promise in the treatment of Vitiligo.
2. All the followings are true for "DVT" except:
   a. Only 40 to 50 percent of patients with DVT have obvious signs and symptoms.
   b. Achilles tendon rupture, cellulitis are the only differential diagnosis of DVT.
   c. Warfarin must be started prior to therapeutic heparinization.
   d. The most severe cases of DVT may require thrombectomy.
3. All the followings are correct for "Childhood Asthma" except:
   a. Asthma affects about 20 percent of child population around the world.
   b. Dry cough, breathlessness are the only presenting features in childhood asthma.
   c. The presence of allergy is not essential to the diagnosis of asthma.
   d. Low birth weight babies are in increased risk of developing asthma.
4. The following features are true for "PCOS" except:
   a. It affects 5 to 10 percent of the population.
   b. PCOS patients tend to obese and insulin resistant.
   c. The miscarriage rate in PCOS is about 20 percent of all pregnancies.
   d. Metformin gives excellent result in PCOS.
5. All the following points are true for "Comet® (Metformin Hydrochloride)" except:
   a. Comet® is used in the patient 10 years of age and above.
   b. Comet XR® must be swallowed whole and never crushed or chewed.
   c. Comet XR® is used in the patient 20 years of age and older.
   d. Comet® should be taken with meals.
6. All the following points are true for "DVT" except:
   a. Blood stress, vascular injury and hypertrophy are collectively known as Virchow's triad.
   b. Varicose veins, pulmonary embolisms are among the complications of DVT.
   c. Acute DVT affects as many as 600,000 new patients per year.
   d. Enoxaparin at therapeutic dose is safe and effective alternative treatment of DVT.

SQUARE in International Business

North Korean Ambassador to Bangladesh HE Mr. Wun Song Mo visited *SQUARE's* manufacturing plant-2 on January 9, 2005. The Ambassador was highly impressed on *SQUARE's* quality commitment & formulation technology.

A delegation from Asian Productivity Organization recently visited *SQUARE's* manufacturing unit-2. They were briefed on the operation and different technical aspects during the visit.

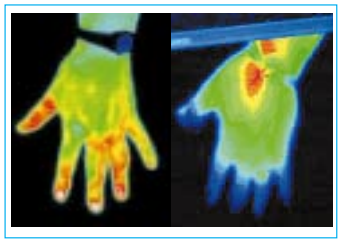
The Chairman and the Managing director of *SQUARE* Pharmaceuticals Ltd. visited *SQUARE's* pavilion during the Asia Pharma Expo 2005 held from 15 to 18 February at Dhaka.

A high level French business delegation visited *SQUARE's* manufacturing facility during their recent tour to Bangladesh.

SQUARE's partner in Tanzania visited *SQUARE's* manufacturing unit-1 during their recent tour to Bangladesh.

Thermal Scans for Arthritis Detection

A device developed to scan computer circuit boards for defects is now being used to detect early signs of arthritis. New technology gives a chance to see something a normal X-ray can't. Using thermal imaging, researchers can tell if someone has early signs of arthritis in the hands. The thermal scanner detects temperature differences. Inflamed joints are warmer-the first sign of arthritis. The thermal scanner is sensitive enough to detect differences of a tenth of a degree in temperature.



Thermal scans showing temperature differences

The researchers hope that if arthritis can be identified earlier, then the doctors have a much easier chance of treating it and preventing those late-stage X-ray changes.

Researchers say thermal scanning for arthritis could become commonplace within five years. They also say thermal technology could also help evaluate the effectiveness of arthritis treatments.

Source: *Ivanhoe.com.*

Synthetic Paste for Tooth Decay!

Treating early tooth decay could become easier and less painful! Researchers in Japan have developed a new synthetic tooth enamel that can repair early tooth decay without the need for drillings and fillings. The crystalline white paste can reconstruct enamel without removing the decayed area. It repairs small cavities and helps prevent new ones. Dentists usually treat cavities by removing the decayed area and filling the hole with a resin or metal alloy. But it is not ideal for small cavities because healthy tooth is also removed to make the filling stick. The scientists tested the new paste on early decay in a lower premolar tooth. After examining the tooth with an electron microscope they found the paste integrated with the tooth's natural enamel.

But the researchers warned the paste should not come into contact with the gums because it could cause inflammation due to its high concentration of hydrogen peroxide.

Source: *Reuters Limited.*

Camera Phone Diagnoses Leg Wounds!

There's another use for those new cell phones that come complete with cameras: diagnosing chronic leg ulceration. Swiss researchers who used the phone cameras to send pictures of wounds to specialists in remote locations say doctors felt fairly comfortable diagnosing the wounds from the photos.

The study involved 52 patients with 61 chronic leg ulcers who were seen in an outpatient clinic. Investigators had a physician on site diagnose the wounds, then sent photos of the wounds to two other physicians at remote locations to get their assessment of the wounds as well. Overall, the remote physicians were able to diagnose the wounds in 82% of the cases. Agreement between the various physicians was high, suggesting the cell phone photos could accurately convey the information doctors need to make a diagnosis.

The researchers plan to conduct additional studies to see how similar teleconsultations could impact patient care under routine conditions.

Source: *Archives of Dermatology, 2005*

New CT Scanner for Heart Disease Diagnosis

A new heart scanner recently installed at Johns Hopkins Medicine has the potential to revolutionize the diagnosis of heart disease. The CT scanner, known as a 64-slice computerized axial tomography scanner, allows physicians to obtain very detailed images of the heart and its surrounding structures in 5 to 10 seconds. It is comparable in quality to the coronary angiogram. Because of its speed, the new CT scanner can be used before patients are stabilized to rapidly diagnose heart attacks and other conditions.

The Hopkins scanner is only the second of its kind in the United States. The other is in Boston, Mass.

Until now, the highest resolution CT scanner was a 32-slice machine. Operating at twice the resolution, the new scanner may make CT scanning a first-line diagnostic choice for the detection and treatment of heart attack and coronary artery disease. Currently, CT scans are usually performed only when necessary. The number of slices is measured by how many x-ray detectors are included in the machine. The greater the number of detectors, the greater the resolution of the resulting scan.

Source: *HealthCentersOnline*

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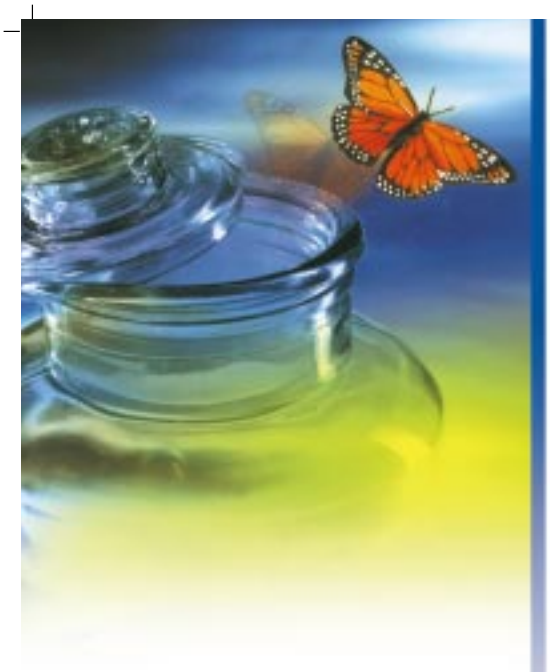

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Salmeterol 25 µg & Fluticasone propionate 250 µg/puff; 120 puffs

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American Heart Association

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Living life free from pain

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