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ZAPORIZHZHIA STATE MEDICAL UNIVERSITY
DEPARTMENT OF GENERAL PRACTICE – FAMILY MEDICINE

THE BASIS OF PREVENTION IN THE PRACTICE OF GENERAL PRACTITIONERS

STUDY GUIDE

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The basis of prevention in the practice of general practitioners : study guide for the practical classes and individual work for 6th-years students of international faculty (speciality «General medicine») Discipline «General practice – family medicine» / N. S. Mykhailovska, A. V. Grytsay. – Zaporizhzhia : ZSMU, 2017. – 224 p.

Study guide compiled in accordance with the program of «General practice - family medicine». Guidelines are intended to help students prepare for practical classes and learn the material. Can be used for training of 6th-years students of international faculty, discipline «General practice - family medicine».

Михайловська Н. С.

Основи профілактики в діяльності лікаря загальної практики : навчально-методичний посібник до практичних занять та самостійної роботи студентів VI курсу міжнародного факультету (спеціальність «Лікувальна справа») з дисципліни «Загальна практика - сімейна медицина» / Н. С. Михайловська, А. В. Грицай. - Запоріжжя: ЗДМУ, 2017. – 224 с.

Навчальний посібник складений відповідно до програми «Загальна практика - сімейна медицина». Видання має на меті сприяти кращому засвоєнню теоретичних знань студентами під час підготовки до практичних занять. Посібник рекомендований для використання студентами VI курсу міжнародного факультету з дисципліни «Загальна практика - сімейна медицина».

CONTENT

PREFACE

Preventive medicine is the efforts directed toward the prevention of disease, either in the community as a whole (an important part of public health) or in the individual. A major preventive role of primary care is to help patients avoid disease or disability.

In the period of rising medical costs, reduced state and federal budgets, and escalating economic difficulties, issues of quality of care, patient safety, and adequate distribution of health care resources are at the forefront of this discussion. As a medical specialty, the preventive medicine is positioned to address these concerns from a basis of clinical evidence to population health.

Study guide is composed according the requirements of typical working program (2009) and working program (2013) of academic discipline «General practice – family medicine», training line 1201 «Medicine». The necessity of this textbook is grounded by absence of such workbooks, which satisfy requirements of basic parts of academic discipline «General practice – family medicine».

The purpose of this study guide is acquiring of knowledge and practical skills of 6^{th}-years students during preparation for classes and final module control.

THE THEMATIC PLAN OF PRACTICAL CLASSES

Module 1: "The organizational aspects of the system of the primary health care in Ukraine, its role in the development and reforming of the Public health."

№	*Topic*	*hours*
Content module 1. ***Modern approaches to the medico-social and organizational basis of a primary health care***		
1.	1.1 The place of the family medicine in the structure of a healthcare system and the principles of the family service. The organization of the FD's work. The basis recording documentation of FD in medical institution. 1.2 The role of information system in FD practice. The basis of information processing of out-patient clinic*	4 3
Content module 2. ***Medico-social aspects of population's health - the basis of the preventive and curing medicine. The organization of out-of-hospital care (pre-hospital and hospital stages)***		
2.	2.1 Medico-social aspects of the population's health. Medical insurance structure and family doctor activity. The models of medical insurance in the world. 2.2 The medical examination of the population, and rehabilitation in the family doctor's practice*	4 3
3.	3.1. The assessment of the risk factors of the main chronic non-epidemic diseases and the preventive measures on the basis of syndrome approach. The national program for prevention, diagnostics and treatment of most widespread diseases. A role of family doctor in popularization of healthy life style and prophylaxis. The dietotherapy. "The health school". 3.2. The prophylaxis of AIDS*	4 3
4.	4.1. The organization of out-of-hospital therapeutic help in case of the most wide-spread diseases. The principles of medico-social expertise. The organization of the day hospital and home care. 4.2. The consultation in the context of HIV-infectious, voluntary testing, before- and after-testing consultation* 4.3. The consultation in the context of incurable disease and imminent death. The organization of medical care for non-curable patients. The principle of multidisciplinary approach to medical care of non-curable patients and their relatives. Nursing, the methods of palliative care of symptoms and syndromes*	4 1,5 1,5
Content module 3. ***The emergency in the family doctor's practice***		
5.	5.1 The emergency at the pre-hospital stage in the case of cardiac arrest, acute coronary syndrome, respiratory standstill, arrhythmias, hypertensic crisis, bronchoobstructive syndrome 5.2 Writing the algorithm of the emergency measures at the pre-hospital stage in the case of cardiac arrest, acute coronary syndrome, respiratory standstill, arrhythmias, hypertensic crisis, bronchoobstructive syndrome: filling the practicum*	4 3
6.	6.1. The emergency in the practice of family doctor in the case of pain syndrome. The clinical classification of pain. 6.2. The mechanism of pain in incurable patient. The principles of treatment of chronic pain syndrome. The emergency in context of incurable diseases and imminent death*	4 3
7.	7.1 The emergency in the practice of family doctor in the case of seizure, syncope, coma in case of diabetes, acute hepatic failure, alcohol intoxication, renal insufficiency, narcotic abuse. 7.2 Writing the algorithm of the emergency measures in the practice of family doctor in the case of seizure, syncope, coma in case of diabetes, acute hepatic failure, alcohol intoxication, renal insufficiency, narcotic abuse: filling the practicum*	4 3
8.	8.1 The emergency in the practice of family doctor in the case of bite, sting, electrical injury, drowning, frostbite and thermal injury. 8.2 Writing the algorithm of the emergency measures in the practice of family doctor in the case of bite, sting, electrical injury, drowning, frostbite and thermal injury: filling the practicum* **Final module control**	4 3 **2**
	Total	**32/ 24***

Note - * marked the theme of individual work performed by students under the teacher's supervision.

THE THEMATIC PLAN

OF INDEPENDENT WORK OF STUDENT

№	*Topic*	*hours*
1	**Preparation for practical classes**	**18**
	The psychological, spiritual and social aspects of palliative care of non-curable patients and their relatives.	4
	The palliative and end-of-life care: the notion, ethical principles.	4
	The organization of medical care for non-curable patients. The methods of palliative care of main symptoms and syndromes	4
	The principle of multidisciplinary approach to medical care of non-curable patients and their relatives. Bad news report The notion about emotional burnout syndrome, its prevention.	2
	The organization of medical care for HIV-infected. The care and psychological support of HIV-infected. The symptomatic treatment of patient in terminal state.	2
	The primary prevention of HIV infections. The preventive HIV-program for different age groups of population.	2
2.	**Practical skills**	**12**
	To fill recording documentations of family doctor	4
	To prepare and fill the management plan for out-patient in the case of most widespread disease.	4
	To create an algorithm of emergency in out-of-hospital stage in the practice of family doctor	4
3.	**The preparation for final module control**	**4**
	Total	**34**

THE BASIS OF PROPHYLAXIS OF WIDESPREAD DISEASES IN THE PRACTICE OF FAMILY DOCTOR

I. Theme actuality. Preventive medicine was established as a specialty to gather physicians working in illness prevention and Public health, to incorporate teaching about these topics into medical school curricula, and to advance opportunities for training in the specialty. Preventive medicine physicians are «uniquely trained in both clinical medicine and Public health. They have the skills needed to understand and reduce the risks of disease, disability, and death in individuals and in population groups». The core disciplines of public health are biostatistics, epidemiology, health policy and administration, health behavior, and environmental health.

Rising levels of obesity and the chronic diseases associated with it characterize the health of public today, driving up our caseloads of cardiovascular disease, diabetes, and cancer. Many infectious diseases controlled during the 20th century through vaccines and antibiotics (tuberculosis, pertussis, and measles) are exhibiting resurgence and being joined by emerging conditions such as HIV/AIDS, severe acute respiratory syndrome (SARS), and the potential for pandemic avian influenza. The threats of man-made and natural disasters such as biological warfare and weather-related events focus attention on how medicine manages to care for large numbers of people who have been injured or don't have access to uncontaminated food and drinking water. These conditions have in common their effects upon large populations rather than on one patient with a given condition.

Preventive medicine consists of measures taken for disease prevention, as opposed to disease treatment. Just as health encompasses a variety of physical and mental states, so do disease and disability, which are affected by environmental factors, genetic predisposition, disease agents, and lifestyle choices. Health, disease, and disability are dynamic processes which begin before individuals realize they are affected. Disease prevention relies on anticipatory actions that can be categorized as primary, secondary, and tertiary prevention.

Each year, millions of people die of preventable deaths.

According to estimates made by the World Health Organization (WHO), about 55 million people died worldwide in 2011, two thirds of this group from non-communicable diseases, including cancer, diabetes, and chronic cardiovascular and lung diseases. This is an increase from the year 2000, during which 60% of deaths were attributed to these diseases. Preventive healthcare is especially important given the worldwide rise in prevalence of chronic diseases and deaths from these diseases.

II. Study purposes: to take up questions of place of preventive medicine in the structure of Public health, the principles of family maintenance of population, to know about organization of work of family doctor.

III. Concrete purposes of the module:

- to find out the place of preventive medicine in the structure of Public health;
- to understand and identify risk factors for the diferent age groups.
- to understand the value of health maintenance and the prevention of illness in terms of its importance to the family doctor and his/her family.
- skilled in the clinical practice of health promotion and disease prevention. Students have to understand principles of evidence-based medicine in order to know which screening tests and interventions are appropriate for their patients.

IV. A student must be able to learn how to incorporate the principles of preventive medicine in a family practice setting.

V. Methodical guidelines for work at the practical level

At the beginning of practical classes the test control of initial knowledge is conducted by the survey according the topic. Under the guidance of teacher the clinical analysis of case histories is conducted with detailized discussion of diagnosis, differential diagnosis, using syndrom’s approach, the clinical work up and treatment plan, emergency for complications. Students are encouraged addressing to the clinical problem. The abstract report of the topic is given by the appropriate presentation. After completion of the class the final test control of knowledge is made. The teacher answers to the questions of students.

PRIMARY AND SECONDARY PREVENTION OF CORONARY ARTERY DISEASE

Despite recent declines in age-adjusted mortality, cardiovascular disease (CVD) has been the leading cause of death and loss of quality life years in the global population. While CVD age-adjusted death rates are reportedly declining in the US, they are increasing in many developing countries. These developing countries and emerging market economies are succumbing to the epidemiologic transition that afflicted the US (CVD-related mortality), posing a major challenge to these regions as they undergo social and economic development as emerging market economies [1].

The most preventable form of CVD is coronary heart disease (CHD). In the US, CHD annually results in 502000 deaths, of which 185000 are due to myocardial infarction (MI); 1,2 million MIs, of which 700000 are first infarctions; and an economic burden of $133 billion. An American Health Association policy statement concluded that costs will rise to more than $1 trillion annually in the US by the year 2030, thus suggesting the great need for preventative measures [2].

Currently, 16,8 million Americans (8,7 million men, 8,1 million women) have documented CHD [1]. Asymptomatic disease is even more prevalent. By the year 2020, CHD is estimated to become the leading cause of death and disability worldwide. Despite this high prevalence, evidence increasingly suggests that the atherosclerotic process can be greatly slowed and its consequences markedly reduced by preventive measures. Primordial prevention usually refers to healthy lifestyle choices to prevent the development of coronary risk factors. Primary prevention deals with delaying or preventing the onset of cardiovascular disease.

Many countries where CHD is on the rise have instituted counselling and educational methods to encourage people to reduce their risks for developing heart disease. Some intervention results in small reductions in risk factors, including blood pressure, cholesterol, and smoking, but has little or no impact on the risk of CHD mortality or morbidity [3]. This demonstrates that a different approach to

behavior change is needed, particularly in developing countries where cardiovascular disease rates are rising.

A lot of US adults with peripheral arterial disease (was defined as an ankle-brachial index of 0,9 or less) are not receiving secondary prevention therapies [4, 5]. Treatment with multiple therapies (statins, ACE inhibitor/angiotensin receptor blockers, and aspirin) is associated with reduced all-cause mortality.

Secondary prevention relies on early detection of disease process and application of interventions to prevent progression of disease (MeSH definition).

Risk Assessment and Primary Prevention

Risk Factors and Risk Scores. Primary prevention reduces MI and heart failure, decreases the need for coronary revascularization procedures, and extends and improves the quality of life. In a 2010 report on cardiovascular risk assessment in asymptomatic adults, it was recommended obtaining global risk scores (eg, Framingham Risk Score) and a family history of cardiovascular disease for cardiovascular risk assessment.

The Framingham Heart Study first introduced the term *risk factor* into modern medical literature; the term is generally applied to a parameter that is predictive of a future cardiovascular event. Broadly, risk factors are arbitrarily divided into 3 major categories:

Table 1

Basic Categories of Risk Factors for Future Cardiovascular Event

Category	**Risk Factors**
Nonmodifiable risk factors	Age, sex, family history, genetic
Modifiable risk factors	Smoking, atherogenic diet, alcohol intake, physical activity, dyslipidemias, hypertension, obesity, diabetes, metabolic syndrome
Emerging risk factors	C-reactive protein (CRP), fibrinogen, coronary artery calcification (CAC), homocysteine, lipoprotein(a), and small, dense LDL

Several risk scores have been developed to help predict an individual's risk of future cardiovascular events. For example, the Framingham Heart Study

developed a coronary risk estimate using some of the following major traditional risk factors:

- Age
- Gender
- Family history of premature CHD (first-degree male relative <55 y, female <65 y)
- Elevated total or LDL cholesterol level
- Reduced HDL cholesterol level
- Smoking
- Hypertension
- Diabetes mellitus
- Obesity
- Sedentary lifestyle.

Using these risk factors, a Framingham score can be computed that helps assess the 10-year risk of CHD for individuals with risk factors. The American Heart Association suggests childhood obesity is likely to lower the age of onset and increase the incidence of cardiovascular disease worldwide.

The differences in risk-factor burden result in marked differences in the lifetime risk for cardiovascular disease. They also conclude that these differences are consistently noted across both race and birth cohorts.

In the following tables diabetes is excluded because it constitutes coronary artery disease risk equivalent.

Table 2

Framingham Point Scores by Age Group in Men

Age	**Points**
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Table 3

Framingham Point Scores by Age Group and Total Cholesterol in Men

Total Cholesterol	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
< 160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
280+	11	8	5	3	1

Table 4

Framingham Point Scores by Age and Smoking Status in Men

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

Table 5

Framingham Point Scores by HDL level in Men

HDL	Points
60+	-1
50-59	0
40-49	1
< 40	2

Table 6

Framingham Point Scores by Systolic Blood Pressure and Treatment Status in Men

Systolic BP	If Untreated	If Treated
< 120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
160+	2	3

Table 7

10-Year Risk by Total Framingham Point Scores in Men

Point Total	10-Year Risk
< 0	< 1%
0	1%
1	1%
2	1%
3	1%
4	1%

5	2%
6	2%
7	3%
8	4%
9	5%
10	6%
11	8%
12	10%
13	12%
14	16%
15	20%
16	25%
17 or more	≥30%

Table 8

Framingham Point Scores by Age Group in Women

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Table 9

Framingham Point Scores by Age Group and Total Cholesterol in Women

Total Cholesterol	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
< 160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
280+	13	10	7	4	2

Table 10

Framingham Point Scores by Age and Smoking Status in Women

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

Table 11

Framingham Point Scores by HDL level in Women

HDL	Points
60+	-1
50-59	0
40-49	1
< 40	2

Table 12

Framingham Point Scores by Systolic Blood Pressure and Treatment Status in Women

Systolic BP	If Untreated	If Treated
< 120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
160+	4	6

Table 13

10-Year Risk by Total Framingham Point Scores in Women

Point Total	10-Year Risk
< 9	< 1%
9	1%
10	1%
11	1%
12	1%
13	2%
14	2%
15	3%
16	4%
17	5%
18	6%
19	8%
20	11%
21	14%
22	17%
23	22%
24	27%
25 or more	≥30%

Prevalence of coronary risk factors in the US is as follows:

- LDL cholesterol >130 mg/dL – 46%
- HDL cholesterol 40 mg/dL – 26%

- Prehypertension – 22%
- Hypertension – 25%
- Tobacco use – 25%
- Diabetes mellitus – 8%
- Overweight or obese – 65%
- Physically inactive – 38%
- Metabolic syndrome – 24%.

Considerable clinical benefit can be derived from the management of 3 major modifiable coronary risk factors: hypercholesterolemia, hypertension, and cigarette smoking.

The addition of CAC scanning to conventional risk factor modification has been associated with superior coronary artery disease risk factor control without increasing downstream medical testing.

Every 1 mmol/L (38,7 mg/dL) decline in LDL cholesterol results in a 21% decrease in cardiovascular events. A decrease in systolic blood pressure by 10 mm Hg can decrease cardiovascular mortality by 20-40%. Similarly, the risk of acute MI increases by 5,6% for every additional cigarette smoked per day.

Screening guidelines. New guidelines from the American Heart Association/American College of Cardiology (AHA/ACC), released in late 2013, recommend use of a revised **calculator** for the risk of developing a first atherosclerotic cardiovascular disease (ASCVD) event, which is defined as one of the following, over a 10-year period, in a person who was initially free from ASCVD:

- Nonfatal myocardial infarction
- Death from coronary heart disease
- Stroke (fatal or nonfatal).

For patients 20-79 years of age who do not have existing clinical ASCVD, the guidelines recommend assessing clinical risk factors every 4-6 years. For patients with low 10-year risk (<7,5%), the guidelines recommend assessing 30-year or lifetime risk in patients 20-59 years old.

Regardless of the patient's age, clinicians should communicate risk data to the patient and refer to the AHA/ACC lifestyle guidelines, which cover diet and physical activity. For patients with elevated 10-year risk, clinicians should communicate risk data and refer to the AHA/ACC guidelines on blood cholesterol and obesity.

Hypercholesterolemia/dyslipidemia. Screening should include a full fasting lipid profile including total cholesterol, HDL, and triglycerides measurements. The ratio of total or LDL cholesterol to HDL appears to be a powerful risk predictor [6].

A primary goal of reducing LDL cholesterol level is as follows:

- <100 mg/dL in individuals with CHD, diabetes, or >20% 10-year Framingham risk;
- <130 mg/dL in individuals with 10-20% 10-year Framingham risk;
- <160 mg/dL in individuals with <10% 10-year Framingham risk.
- Secondary goals are as follows:
- If LDL goals are achieved and triglyceride levels are >200 mg/dL, the goal for non-HDL cholesterol level should be set at 30 mg/dL higher than the LDL cholesterol level.
- In response to the recent trial results, the NCEP has recommended lowering of the LDL target goals to <70 mg/dL with at least 30-40% reduction for very high-risk individuals, such as those with ACS or diabetes and to <100 mg/dL for those at moderately high risk [6].
- Measurement of HDL cholesterol should be used as part of the initial cardiovascular risk assessment but should not be used as a predictive tool of residual vascular risk in patients who are treated with potent high-dose statin therapy to lower LDL cholesterol [6].
- The extended follow-up of the Heart Protection Study assessed the long-term efficacy and safety of lowering LDL cholesterol with statins, and found that prolonged LDL-lowering statin treatment produces larger absolute reductions in

vascular events. The benefits of long-term continuation of statin treatment persisted for at least 5 years without any evidence of developing risks [6].

- European health authorities have suggested that when LDL cholesterol levels do not require pharmacologic treatment, 20 mg of rosuvastatin significantly reduces major cardiovascular events in primary prevention patients with elevated high-sensitivity C-reactive protein who have high global cardiovascular risk (10-year Framingham risk score >20%) [6].
- The Multi-Ethnic Study of Atherosclerosis (MESA) studied eligible participants from the JUPITER trial to assess whether or not coronary artery calcium (CAC) might further stratify risk. The results suggest that CAC could be used to target subgroups of patients who are expected to derive the most, and the least, absolute benefit from statin treatment [7].

The 2013 AHA/ACC guidelines on the management of elevated blood cholesterol no longer specify LDL- and non-HDL-cholesterol targets for the primary and secondary prevention of atherosclerotic cardiovascular disease. The new guidelines identify four groups of primary- and secondary-prevention patients in whom efforts should be focused to reduce cardiovascular disease events and recommend appropriate levels of statin therapy for these groups [7].

Treatment recommendations include the following:

- In patients with atherosclerotic cardiovascular disease, or those with LDL cholesterol levels 190 mg/dL or higher (eg, due to familial hypercholesterolemia), and no contraindications, high-intensity statin therapy should be prescribed to achieve at least a 50% reduction in LDL cholesterol.
- In patients aged 40 to 75 years of age with diabetes, a moderate-intensity statin that lowers LDL cholesterol by 30% to 49% should be used; in those patients who also have a 10-year risk of atherosclerotic cardiovascular disease exceeding 7,5%, a high-intensity statin is a reasonable choice.
- In individuals aged 40 to 75 years without cardiovascular disease or diabetes but with a 10-year risk of clinical events >7,5% and an LDL-cholesterol level of 70-189 mg/dL, a moderate- or high-intensity statin should be used.

Secondary causes of dyslipidemia. Before therapy is initiated, the following potential secondary causes of dyslipidemia should be considered based on the associated dyslipidemia:

- High LDL: Hypothyroidism, nephrotic syndrome, primary biliary cirrhosis, and anorexia nervosa.
- Hypertriglyceridemia: Diabetes mellitus, chronic kidney disease, alcoholism, pregnancy, hypothyroidism.
- Low HDL: Diabetes mellitus, cigarette smoking, obesity [8].

Table 14

Proposed Modifications of ATP III LDL-Cholesterol Goals and Cut Points for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal	LDL level at which to Initiate Therapeutic Lifestyle Changes	LDL level at which to Consider Drug Therapy
High risk - CHD or CHD risk equivalent (10-y risk >20%)*	< 100 mg/dL; optional goal < 70 mg/dL in very high risk**	≥100 mg/dL‖	≥100 mg/dL,¶ < 100 mg/dL consider drug options
Moderate-high risk - 2 or more risk factors (10-y risk 10-20%)†	< 130 mg/dL††	≥130 mg/dL	≥130 mg/dL; 100-129mg/dL consider drug options#
Moderate risk – 2 or more risk factors (10-year risk < 10%)	< 130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk – 0-1 risk factor‡	< 160 mg/dL	≥160 mg/dL	≥190 mg/dL; 160-189 mg/dL consider drug options

* Heart disease risk equivalents include noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease) and diabetes. Ten-year risk defined by modified Framingham risk score.

† Risk factors that modify LDL goals include cigarette smoking; hypertension (BP ≥140/90 mm Hg or on antihypertensive medications); low HDL cholesterol (<40 mg/dL); family history of premature CHD (CHD in male first-degree relative <55 y or in female first-degree relative <65 y); and age (men ≥45 y, women ≥55 y). HDL cholesterol ≥60 mg/dL counts as a negative risk factor; its presence removes 1 risk factor from the total count.

‡ Almost all people with 0-1 risk factor have a 10-year risk of less than 10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

[§] When LDL-lowering drug therapy is given, the intensity of therapy should be sufficient to achieve at least a 30-40% reduction in LDL levels.

[‖] Any individual at high or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, hypertriglyceridemia, low HDL cholesterol [<40 mg/dL], or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors independent of LDL level.

[¶] If baseline LDL is <100 mg/dL, institution of an LDL-lowering drug is an option. This can be combined with a fibrate or nicotinic acid if a high-risk person has a hypertriglyceridemia or low HDL (<40 mg/dL).

[#] For moderately high-risk persons with LDL of 100-129 mg/dL at baseline or after lifestyle changes, initiation of an LDL-lowering drug to achieve an LDL of less than 100 mg/dL is an option.

[**] Very high risk favors the optional LDL goal of <70 mg/dL and, in patients with high triglycerides, non-HDL cholesterol goal of < 100 mg/dL.

[††] Optional LDL goal of <100 mg/dL.

Triglycerides. Data on the impact of triglycerides on CHD events is not as clearly evident. However, meta-analyses data suggest that elevated triglyceride levels are an independent risk factor for CHD, and data on the benefits of reducing triglyceride levels were demonstrated by using the drug gemfibrozil (fibric acid derivative) in a population with low HDL level (<40 mg/dL) [9].

Non-HDL cholesterol. In patients with mixed dyslipidemia (elevated LDL cholesterol and triglyceride levels), non-HDL cholesterol is a useful measurement. Non-HDL cholesterol represents very LDL cholesterol plus LDL cholesterol, both of which are apo B-100-containing atherogenic lipoprotein fractions. In hypertriglyceridemic individuals, non-HDL cholesterol goals are 30 mg/dL higher than the corresponding LDL goals, representing a triglyceride goal of 150 mg/dL. Non-HDL cholesterol can be measured in a nonfasting state. Non-HDL cholesterol was found to be more predictive of future CV events than LDL in several trials, probably because it measures both of the atherogenic apo B-containing fractions [9]. LDL and total cholesterol/HDL cholesterol ratios are also strongly predictive of CVD risk.

Secondary prevention

When drug therapy is indicated for reducing LDL-cholesterol, statins are generally initiated as first-line therapy. Exceptions include pregnancy, hepatic disease, or history of myositis while on these agents. Resins, nicotinic acid, or

ezetimibe can be added if LDL cholesterol level is not reduced to goal. Pharmacologic therapy for triglyceridemia includes fibrates, nicotinic acid, and omega-3 fatty acids. Fibrates and nicotinic acid are also effective in raising low HDL, particularly when high triglycerides are present.

In mixed dyslipidemias, a statin may be combined with nicotinic acid or a fibrate. Non-HDL cholesterol is a useful parameter to monitor therapy results in mixed dyslipidemia. When using combined therapy, particularly statins plus fibrates, the risk of myositis increases and patients should be educated about muscle symptoms. To minimize the risk of statin myopathy, the statin dose should be kept as low as possible to achieve the LDL goal, and it may be helpful to separate the dosing of statins and fibrates to evening and morning, respectively.

Varespladib methyl 500 mg once daily may be an effective antiatherosclerotic agent. Compared with placebo or statin monotherapy, evacetrapib as monotherapy or in combination with statins increased HDL-C levels and decreased LDL-C levels. However, further investigation is warranted.

Blood Pressure Control. Hypertension is a well-established risk factor for adverse cardiovascular outcomes, including CHD. Systolic blood pressure is at least as powerful a coronary risk factor as the diastolic blood pressure. Isolated systolic hypertension is now established as a major hazard for CHD. Compelling data from meta-analyses indicate that a reduction of diastolic blood pressure by 5-6 mmHg results in a reduction of stroke risk by 42% and CHD events by 15% [10].

The self-management of hypertension, which includes self-monitoring of blood pressure and self-titration of antihypertensive drugs, along with telemonitoring of home blood pressure measurements, is an important new addition to the control of hypertension in primary care. Patients who self-manage hypertension have experienced a decrease in systolic blood pressure compared to those who sought usual care. The wireless remote monitoring with automatic clinician alerts significantly reduced the time to a clinical decision in response to clinical events as well as reduced the length of hospital stay [10].

In patients with mild hypertension (systolic 140-159 mmHg or diastolic 90-99 mmHg), the following is noted:

- Despite side effects and cost of antihypertensive medications, the beneficial effects of treatment may outweigh the risks, even in low-risk patients.
- Treatment, if necessary, is initiated with a low-dose of a once-a-day antihypertensive drug in an attempt to minimize future cardiovascular risk after a prolonged trial of nonpharmacologic therapy.
- One such antihypertensive medication that is used worldwide is hydrochlorothiazide (HCTZ). A daily dose of 12,5-25 mg was shown to be consistently inferior to all other drug classes. Because data is lacking for dosing, HCTZ is an inappropriate first-line drug for the treatment of hypertension.
- In individuals with high-normal blood pressure (systolic 130-139 mm Hg and/or diastolic 85-89 mm Hg), the following is noted:
- These persons have an increased risk of cardiovascular events over time compared with those who have optimal blood pressure.
- Antihypertensive drug therapy should be considered among such patients if diabetes or end-organ damage is present.
- Treatment, particularly with an angiotensin-converting enzyme (ACE) inhibitor or, if not tolerated, an angiotensin-II receptor blocker, is also warranted in patients with renal insufficiency, diabetes mellitus, or heart failure to slow the progression of the underlying disease.

Diet. Two types of dietary guidelines exist. The first type recommends specific quantities of macronutrients, such as <200 mg of cholesterol per day and <7% of calories as saturated fat, as in the AHA Step 2 diet [10].

A second type recommends the consumption and exclusion of specific foods, often in combination. An example is the recommendation to eat the following foods to lower cholesterol: stanol/sterol ester margarines, soy products, soluble fiber, and almonds or walnuts. This specific food portfolio recommendation has been found to lower LDL cholesterol more than an AHA Step 2 approach (29% vs 8%, respectively). The reductions were, in fact, equivalent to

those of lovastatin 20 mg [10]. Total allowed daily fat ranges from 25-35% of total daily calories provided that saturated fats and trans-fatty acids are kept low.

A diet containing stanol-enriched margarine, soy products, high-fiber foods, and almonds reduced LDL cholesterol and CRP more than an NCEP diet. The reductions were equivalent to lovastatin 20 mg.

The Third ATP of the NCEP further modified its dietary recommendations to include a more intense and effective eating plan than previously advocated. Specific recommendations are as follows:

1) Saturated fat <7% of total calories,

2) polyunsaturated fat, about 10% of total calories,

3) monounsaturated fat, about 20% of total calories,

4) total fat, about 25-35% of total calories,

5) carbohydrates, about 50-60%,

6) fiber, about 20-30 g/d,

7) protein, about 15% of total calories,

8) cholesterol < 200 mg/d.

In general, diets containing unsaturated fats, whole grains, fruits, vegetables, fish, and moderate alcohol are optimal for preventing heart disease. The revised AHA guidelines place emphasis on foods and an overall eating pattern, rather than on percentages of food components such as fat.

One meta-analysis studied the effect of a Mediterranean diet on metabolic syndrome. The diet is characterized by high consumption of monounsaturated fatty acids, primarily from olives and olive oil, and encourages daily consumption of fruits, vegetables, whole grain cereals, and low-fat dairy products; weekly consumption of fish, poultry, tree nuts, and legumes; a relatively low consumption of red meat, approximately twice a month; as well as a moderate daily consumption of alcohol, normally with meals. Adherence to the diet was associated with reduced risk of metabolic syndrome and reduced HDL-cholesterol levels and triglycerides levels. The results are of considerable public health

importance because this dietary pattern can be easily adopted by all population groups and various cultures and is cost-effective.

The Mediterranean diet had more favorable changes in weighted mean differences of body weight, body mass index, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol, and high-sensitivity C-reactive protein than low-fat diets [11].

Of note, in a recently published prospective study, dietary supplementation with marine omega-3 fatty acids (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA] and the plant-derived alpha-linolenic acid [ALA]) did not significantly reduce the rate of cardiovascular events among patients with a prior myocardial infarction [11].

Alcohol. Moderate alcohol consumption (1-2 drinks per d) is associated with a reduced overall and CHD-related mortality compared with both abstinence and heavy drinking [12].

However, alcohol raises HDL (by stimulating the hepatic production of apo A-I and A-II), stimulates fibrinolysis [13], reduces fibrinogen levels, reduces inflammation, and inhibits platelet activation. Moreover, the personal and social risks of alcohol intake (eg, violence, trauma, car accidents, binge drinking) appear to be higher in younger individuals [14].

The additional antioxidant effects have been attributed to red wine, but the consumption of other alcoholic beverages is associated with a somewhat lower or similar reduction in CHD risk [14], and the pattern and amount of alcohol intake appears to be more important than the type.

Antioxidants. Although several studies found reduced CVD in those taking large amounts of antioxidant vitamins, the HOPE GISSI-Prevention, and Heart Protection Studies (HPS) found no benefit for 400 and 300 IU/d of vitamin E, respectively [5].

A current meta-analysis of available data suggests no benefit for antioxidant vitamins [15].

Herbals. An estimated 40% of Americans use herbal remedies, and at least $15 billion is spent annually on alternative forms of health care. Inquiry about the use of herbals is a component of good medical care, especially in cardiovascular medicine.

Alternative medicine approaches to cholesterol lowering include garlic, policosanol, gugulipid, and red rice yeast extracts, the latter of which contains HMG-CoA reductase inhibitors. Garlic modestly lowers cholesterol (approximately 3%) and may lower BP and inhibit platelet aggregation. Fermented red rice yeast extracts contain statins and lower cholesterol 13-26%. Ephedra-containing herbals, often used as anorexics, are associated with hypertension and stroke and have been banned in the US [15].

Summary of General Nutritional Recommendations. Achieve and maintain ideal body weight by limiting foods high in calories and low in nutrition, including those high in sugar, such as soft drinks and candy.

Eat a variety of fruits; vegetables; legumes; nuts; soy products; low-fat dairy products; and whole grain breads, cereals, and pastas.

Eat baked or broiled fish at least twice per week.

Choose oils and margarines low in saturated fat and high in omega-3 fat, such as canola, soybean, walnut, and flaxseed oils, including those fortified with stanols and sterols.

Avoid foods high in saturated and trans-fats, such as red meat, whole milk products, and pastries.

Limit alcohol consumption to no more than 2 drinks per day for a man or 1 drink per day for a woman.

Eat less than 6 g of salt or <2400 mg/d of sodium.

Physical Activity. Reduced physical activity is a major risk factor for CVD. In elderly individuals, the risk of MI is reduced by as much as 50% by walking 30 minutes daily. A study of the associations between physical activity and risk of cardiovascular disease among 44551 middle-aged men found vigorous- and

moderate-intensity activity were associated with lower risk of disease. Low fitness in mid-life was associated with higher lifetime risk for CVD death [16].

Abnormal heart rate recovery (HRR) has been shown to predict mortality. A study by Jolly et al to determine whether HRR could be improved with cardiac rehabilitation suggests it can improve after patients with abnormal HRR at baseline normalize HRR with exercise. The mortality rate was similar to that of individuals with baseline normal HRR [16].

The following general principles need to be considered in recommending increased physical activity:

- Increased physical activity begins with increasing lifestyle activities, such as walking.
- A complete exercise program includes aerobic exercise, resistive training, and stretching.
- More frequent exercise, optimally daily, provides more benefit.
- More strenuous exercise, such as jogging, provides more benefit. A good goal is 75% of age-predicted maximal heart rate (220 - age of individual).
- Excellent benefit can be derived from 30 minutes of daily exercise.
- Even 15 minutes a day or 90 minutes a week of moderate-intensity exercise may be beneficial.
- The most recent scientific statement from the AHA provides recommendations on implementing the most efficacious and effective physical activity and dietary strategies in adults.
- Elevated waist circumference and physical inactivity are associated with an increased risk of coronary heart disease [16].

Smoking. Of all the lifestyle modifications recommended to prevent CVD, smoking cessation is the most important. Smoking cessation is the most cost-effective preventive measure, estimated at $220 per year of life saved. Individuals aged 30 years gain 3-5 years of life by stopping smoking and the mortality benefit was equally impressive in elderly populations. The most effective smoking cessation programs involve programmatic and/or group support and the use of

nicotine substitutes and antidepressants, such as bupropion. Varenicline is a recent addition to the armamentarium and has been found to be superior to bupropion in this respect [17].

Smoking is a risk factor for CVD in women and men; however, in some countries, smoking by women is on the rise; proper counseling and nicotine addiction programs should focus on young women [17].

Smoking cessation counseling with supportive contact after a patient with acute myocardial infarction is discharged is potentially cost-effective and may reduce the incidence of smoking and further adverse health events.

Secondary prevention (after development of CHD)

Table 15

Smoking Cessation and Mortality After MI [96]

Study	**Patients Studied (No.)**	**5-Year Mortality Rate**	
		Quitters	**Smokers**
Sparrow, 1978	365 (269 men, 96 women)	12%	25%
Aberg, 1983	983 (men only)	16%	22%
Daly, 1983	498 (men only)	20%	30%
Johansson, 1985	156 (women only)	15%	27%
Perkins, 1985	119 (90 men, 29 women)	21%	47%
Hedback, 1987	305 (258 men, 47 women)	16%	31%

Several large observational studies showed a substantial reduction in mortality [RR: 0,64 (I: 0,58-0,71)] in patients with a history of MI, CABG, angioplasty, or known CHD, who quit smoking compared with patients who continued to smoke. The overall mortality risk of smokers who quit decreases by 50% in the first couple of years and tends to approach that of nonsmokers in approximately 5-15 years of cessation of smoking.

Primary prevention should start with lifestyle modification, including weight management, diet, physical activity, and smoking cessation. Hormone therapy increases cardiovascular events in postmenopausal women. Estrogen alone increases stroke, but it does not alter CHD events.

Aspirin. Two meta-analyses showed that aspirin use (75-162 mg/d) decreases the occurrence of primary MI by 25-33% and has also been shown to decrease death due to vascular causes; these benefits are not gender specific [98,

99]. However, all benefits have to be balanced against the risk of GI bleeding. Low-dose aspirin therapy (75 mg/d) is therefore recommended for primary prevention in individuals with a 10-year Framingham coronary risk estimate greater than 10%, outweighing risks of gastrointestinal hemorrhage and hemorrhagic stroke. Aspirin has been shown to be similarly efficacious in secondary prevention of MI, stroke, and death secondary to vascular causes. However, others suggest aspirin has only modest benefit in patients without clinical cardiovascular disease and this benefit is offset by its risk [18].

Classification of Recommendations

Recommendations made herein are based largely on major practice guidelines from the National Institutes of Health and ACC/AHA. The information presented is adapted from recent statements by the AHA/ACC, which involved the process of partial adaptation of other guideline statements and reports and supplemental literature searches. The American College of Cardiology Foundation (ACCF) and AHA has produced guidelines for the procedures of detection, management, or prevention of disease [18].

Classification of recommendations and level of evidence is as follows:

- Class I - Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective
- Class II - Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
    - ✓ Class IIa - Weight or evidence/opinion is in favor or usefulness/efficacy
    - ✓ Class IIb - Usefulness/efficacy is less well established by evidence/opinion
- Class III - Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful

Level of evidence is as follows:

- Level of evidence A - Data derived from multiple randomized clinical trials or meta-analyses
- Level of evidence B - Data derived from single randomized trial or nonrandomized studies
- Level of evidence C - Only consensus opinion or experts, case studies, or standard-of-care

Secondary Prevention Goals and Management

Patients covered by these guidelines include those with established coronary and other atherosclerotic vascular disease, including peripheral arterial disease, atherosclerotic aortic disease, and carotid artery disease. Treatment for patients whose only manifestation of cardiovascular risk is diabetes will be the topic of a separate AHA scientific statement.

The AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update: A Guideline From the AHA and ACCF has been released.

Smoking cessation. The goal is complete cessation and no exposure to environmental tobacco smoke.

- Ask the patient about tobacco use status at every visit. **I (B)**
- Advise every patient who uses tobacco to quit. **I (B)**
- Assess the patient's willingness to quit using tobacco. **I (B)**
- Assist the patient by counseling and developing a plan for quitting. **I (B)**
- Arrange follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and bupropion). **I (B)**
- Urge the patient to avoid exposure to environmental tobacco smoke at work and home. **I (B)**

Blood pressure control. The goal is BP <140/90 mmHg or <130/80 mmHg if the patient has diabetes or chronic kidney disease.

For all patients, initiate or maintain lifestyle modification, weight control, increased physical activity, alcohol moderation, sodium reduction, and increased consumption of fresh fruits, vegetables, and low-fat dairy products - **I (B)**

For patients with BP ≥140/90 mmHg (or 130/80 mmHg for individuals with chronic kidney disease or diabetes), as tolerated, add BP medication, treating initially with beta-blockers and/or ACE inhibitors, with addition of other drugs, such as thiazides, as needed to achieve goal blood pressure - **I (A)**

Diet that includes nonhydrogenated unsaturated fats as the predominant form of dietary fat, whole grains as the primary form of carbohydrate, fruits and vegetables, omega-3 fatty acids (from fish, fish oil supplements, or plant sources) offer significant protection against coronary heart disease.

Light-to-moderate alcohol consumption (5-25 g/d) has been significantly associated with a lower incidence of cardiovascular and all-cause mortality in patients with cardiovascular disease. One meta-analysis found J-shaped curves for alcohol consumption and mortality, with a significant maximal protection against cardiovascular mortality with consumption of approximately 26 g/d and maximal protection against mortality from any cause in the range of 5-10 g/d [19].

Lipid management. The goal is LDL cholesterol <100 mg/dL; if triglyceride levels are ≥200 mg/dL, non-HDL cholesterol should be <130 mg/dL. (Non-HDL cholesterol is total cholesterol minus HDL cholesterol.)

The following measures should be taken for all patients:

- Start dietary therapy. Reduce the intake of saturated fats (to <7% of total calories), trans-fatty acids, and cholesterol (to <200 mg/d) - **I (B)**
- Adding plant stanol/sterols (2 g/d) and viscous fiber (>10 g/d) will further lower LDL cholesterol level.
- Promote daily physical activity and weight management - **I (B)**
- Encourage increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1 g/d) for risk reduction (Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury)
- For treatment of elevated triglyceride levels, higher doses are usually necessary for risk reduction - **IIb (B)**

To encourage treatment compliance, particularly with cardiovascular medications in secondary prevention, physician should provide not only clear

discussions about the risk of disease recurrence and medication-specific information at the start of pharmacotherapy, but they should ease the transition between primary and secondary care [19].

Assess fasting lipid profile in all patients and within 24 hours of hospitalization for those with an acute cardiovascular or coronary event. For hospitalized patients, initiate lipid-lowering medication as recommended below before discharge according to the following schedule:

- LDL cholesterol level should be <100 mg/dL. **I (A)**
- Further reduction of LDL cholesterol level to <70 mg/dL is reasonable. **IIa (A)**
- If baseline LDL cholesterol level is 100 mg/dL, initiate LDL-lowering drug therapy. **I (A)**
- If the patient is on treatment and LDL cholesterol is 100 mg/dL, intensify LDL-lowering drug therapy (may require LDL-lowering drug combination [standard dose of statin with ezetimibe, bile acid sequestrant, or niacin]). **I (A)**
- If baseline LDL cholesterol level is 70-100 mg/dL, treating to LDL cholesterol level of <70 mg/dL is reasonable. **IIa (B)**
- If triglyceride levels are 200-499 mg/dL, non-HDL cholesterol level should be <130 mg/dL. **I (B)**
- Further reduction of non-HDL cholesterol level to <100 mg/dL is reasonable. **IIa (B)**

Therapeutic options to reduce non-HDL cholesterol level are as follows:

- More intense LDL cholesterol-lowering therapy, **I (B)**
- Niacin (after LDL cholesterol-lowering therapy), **IIa (B)**
- Fibrate therapy (after LDL cholesterol-lowering therapy), **IIa (B)**

If triglyceride levels are 500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL-lowering therapy, and treat LDL cholesterol level to goal after triglyceride-lowering therapy. Achieve non-HDL cholesterol level of <130 mg/dL if possible. **I (C)** (Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrant is

relatively contraindicated when triglycerides are >200 mg/dL) (The combination of high-dose statin plus fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination. Dietary supplement niacin must not be used as a substitute for prescription niacin.).

The AIM HIGH study selected patients at risk for cardiovascular events despite well-controlled LDL («bad cholesterol»). Participants who took high-dose, extended-release niacin and statin treatment had increased HDL cholesterol and lower triglyceride levels compared with participants who took a statin alone; however, but the combination treatment did not reduce fatal or nonfatal heart attacks, strokes, hospitalizations for acute coronary syndrome, or revascularization procedures to improve blood flow in the arteries of the heart and brain.

The patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of less than 70 mg/dL (1,81 mmol/L) experienced no incremental clinical benefit from the addition of niacin to statin therapy, despite significant improvements in HDL cholesterol and triglyceride levels.

Intensive statin dosing reduces the risk of nonfatal events (coronary heart disease and nonfatal myocardial infarction) and may have a role in reducing mortality. However, the benefits of high-dose statins must be weighed against the risk of myopathy, including rhabdomyolysis, at high doses.

When LDL-lowering medications are used, obtain at least a 30-40% reduction in LDL cholesterol levels. If LDL cholesterol <70 mg/dL is the chosen target, consider drug titration to achieve this level to minimize side effects and cost. When LDL cholesterol <70 mg/dL is not achievable because of high baseline LDL cholesterol levels, it generally is possible to achieve reductions of >50% in LDL cholesterol levels by either satins or LDL cholesterol-lowering drug combinations.

Lowering LDL cholesterol with statin regimens may have an effect in people with moderate-to-severe kidney disease. The Study of Heart and Renal Protection (SHARP) Trial suggests simvastatin (20 mg) plus ezetimibe (10 mg) daily safely

reduces the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease.

Secondary prevention trials in older persons with CAD and hypercholesterolemia have demonstrated that statin drugs reduced all-cause mortality, cardiovascular mortality, coronary events, coronary revascularization, stroke, and intermittent claudication. Statin therapy significantly decreases cardiovascular events and all-cause mortality in both women and men [20].

Lipid-lowering therapy is associated with delayed cardiovascular events and prolonged survival in patients with homozygous familial hypercholesterolemia.

Physical activity. The goal of physical activity is 30 minutes, 7 days per week (minimum 5 d/w). The US guidelines for physical activity suggest low, moderate, and high activity levels. A meta-analysis by Sattlemair et al. attempted to quantify these amounts and found that «some physical activity is better than none» and «additional benefits occur with more physical activity» [21].

- For all patients, assess risk with a physical activity history and/or an exercise test to guide prescription - **I (B)**
- For all patients, encourage 30-60 minutes of moderate-intensity aerobic activity (eg, brisk walking) on most, preferably all, days of the week, supplemented by an increase in daily lifestyle activities (eg, walking breaks at work, gardening, household work) - **I (B)**
- Encourage resistance training 2 days per week - **IIb (C)**
- Advise medically supervised programs for high-risk patients (eg, recent acute coronary syndrome or revascularization, heart failure) - **I (B)**

Weight management. The goal of weight management is body mass index of 18,5-24,9 kg/m^2 and waist circumference of <40 inches in men and <35 inches in women. The AHA released a Scientific Statement in 2011 regarding weight management strategies for busy ambulatory surgery settings [22].

- Assess body mass index and/or waist circumference on each visit and consistently encourage weight maintenance or reduction through an appropriate balance of physical activity, caloric intake, and formal

behavioral programs when indicated to maintain or achieve a body mass index between 18,5 and 24,9 kg/m^2. **I (B)**

- If waist circumference (measured horizontally at the iliac crest) is 35 inches in women and 40 inches in men, initiate lifestyle changes and consider treatment strategies for metabolic syndrome as indicated. **I (B)**
- The initial goal of weight loss therapy should be to reduce body weight by approximately 10% from baseline. With success, further weight loss can be attempted if indicated through further assessment. **I (B)**

Maintaining or improving fitness is associated with a lower risk of all-cause and CVD mortality in men. Health care providers should encourage men to exercise regularly, regardless of age, as it is important for longevity regardless of BMI change [22].

Diabetes management. The goal of diabetes management is to maintain glycosylated hemoglobin (HbA1c) concentration of <7%.

- Initiate lifestyle and pharmacotherapy to achieve near-normal HbA1c level - **I (B)**
- Begin vigorous modification of other risk factors (eg, physical activity, weight management, BP control, and cholesterol management) as recommended above. **I (B)**
- Coordinate diabetic care with the patient's primary care physician or endocrinologist - **I (C)**

Antiplatelet agents and anticoagulants:

- Start aspirin 75-162 mg/d, and continue indefinitely in all patients unless contraindicated - **I (A)**
- For patients undergoing coronary artery bypass grafting, aspirin should be started within 48 hours after surgery to reduce saphenous vein graft closure. Dosing regimens ranging from 100-325 mg/d appear to be efficacious. Doses higher than 162 mg/d can be continued for up to 1 year - **I (B)**
- Start and continue clopidogrel 75 mg/d in combination with aspirin for up to 12 months in patients after acute coronary syndrome or percutaneous

coronary intervention with stent placement (at least 1 month, but ideally 12 months, for bare metal stent; at least 12 months for drug-eluting stents). **I(B)**

- Patients who have undergone percutaneous coronary intervention with stent placement should initially receive higher-dose aspirin at 162-325 mg/d for 1 month for bare metal stent, 3 months after sirolimus-eluting stent, 6 months after paclitaxel-eluting stent, after which daily long-term aspirin use should be continued indefinitely at a dose of 75-162 mg [120] - **I (B)**
- Manage warfarin to international normalized ratio of 2,0-3,0 for paroxysmal or chronic atrial fibrillation or flutter, and in post-MI patients when clinically indicated (eg, atrial fibrillation, left ventricular thrombus) - **I (A)**
- Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closelym- **I (B)**

A nationwide cohort study suggests NSAID treatment duration in patients with prior myocardial infarction, whether short term or long term, is associated with increased risk of death and recurrent myocardial infarction in patients with prior myocardial infarction and is not recommended for this population. NSAID use should be limited from a cardiovascular safety point of view.

Renin, angiotensin, and aldosterone system blockers. Consider the following with ACE inhibitors:

- Start and continue indefinitely in all patients with left ventricular ejection fraction ≥40% and in those with hypertension, diabetes, or chronic kidney disease, unless contraindicated. **I (A)**
- Consider for all other patients. **I (B)**
- Among lower-risk patients with normal left ventricular ejection fraction in whom cardiovascular risk factors are well controlled and revascularization has been performed, use of ACE inhibitors may be considered optional. **IIa (B)**

Consider the following with angiotensin receptor blockers:

- Use in patients who are intolerant of ACE inhibitors and have heart failure or have had an MI with left ventricular ejection fraction ≤40%. **I (A)**

- Consider in other patients who are intolerant of ACE inhibitors. **I (B)**
- Consider use in combination with ACE inhibitors in systolic dysfunction heart failure. **IIb (B)**

Aldosterone blockade are used in post-MI patients without significant renal dysfunction (creatinine should be >2,5 mg/dL in men and >2,0 mg/dL in women) or hyperkalemia (potassium should be <5 mEq/L), who are already receiving therapeutic doses of an ACE inhibitor and beta-blocker, have left ventricular ejection fraction ≤40%, and have either diabetes or heart failure. One study suggests that higher dietary potassium intake is associated with lower rates of stroke and may reduce the risk of coronary heart disease [23]. **I (A)**

Beta-blockers:

- Start and continue indefinitely in all patients who have had MI, ACS, or LV dysfunction with or without heart failure symptoms, unless contraindicated. **l (A)**
- Consider chronic therapy for all other patients with coronary or other vascular disease or diabetes, unless contraindicated. **lla (C)**

Influenza vaccination. Patients with cardiovascular disease should have an influenza vaccination. **I (B)**

Women and Coronary Artery Disease. In the US, CHD is the leading cause of death in both men and women, claiming more lives than cancer, accidents, and diabetes combined [24]. Although breast cancer may be more feared, age-adjusted death rates from CVD in women are 4 times higher in white women and 6 times higher in black women than the death rates for breast cancer.

The 2010 ACCF/AHA report on assessment of cardiovascular risk in asymptomatic adults includes the recommendation that for all adult women and men, global risk scoring should be performed and a family history of cardiovascular disease should be obtained for cardiovascular risk assessment [5].

Compared with men, LDL cholesterol is lower and HDL cholesterol is higher in women before menopause. Although women have lower rates of hypertension and cigarette smoking than men, rates for obesity and diabetes

mellitus are higher. Diabetes mellitus is a particularly serious risk factor in women, tripling the risk of cardiovascular death and causing diabetic women to have the same frequency of CVD as diabetic men [25]. HDL cholesterol and triglyceride levels are more predictive of CVD in women than in men. Women have been noted to have similar or slightly higher prevalence of stable angina as compared to men.

It is now known that women tend to present more commonly with unstable angina as compared to men, the reverse of which is true for MI. However, when women do present with MI, they are more likely to have Q wave rather than non-Q wave. Mortality rates of MI and CABG are about 50% higher in women, mostly related to older age of onset. Lipid lowering has shown similar efficacy in women and men in the angiographic progression and event trials. Cardioprotective agents, including aspirin, beta-blockers, and ACE inhibitors, appear to have similar efficacy in men and women.

Hormone therapy is no longer recommended to prevent coronary events in postmenopausal women with or without established CHD. Although hormone therapy improves LDL and HDL cholesterol levels, it also increases coagulation and inflammation (as measured by C-reactive protein [CRP]) and decreases LDL particle size [1, 26]. Treatment rates for risk factors in women tend to be even lower than in men, as are rates for coronary angiography and coronary artery revascularization following presentation with chest pain.

Finally, it must be emphasized that while the guidelines detailed above represent best practice, their formulation is often a blend of science and art. Therefore, guideline interpretation should always occur alongside good clinical judgment.

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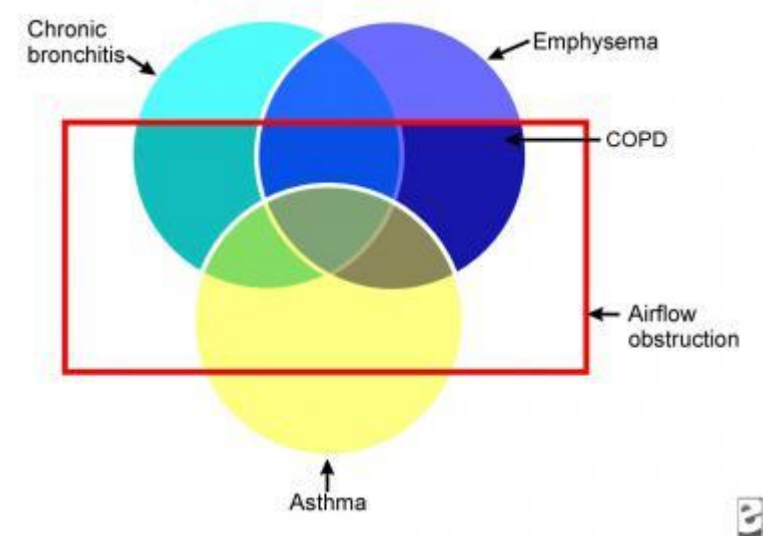
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Background. Chronic obstructive pulmonary disease (COPD) is estimated to affect 32 million persons in the US and is the third leading cause of death in this country [1]. Patients typically have symptoms of chronic bronchitis and emphysema, but the classic triad also includes asthma (seen in the image below).



Venn diagram of COPD. COPD is a disorder in which subsets of patients may have dominant features of chronic bronchitis, emphysema, or asthma. The result is airflow obstruction that is not fully reversible.

Chronic bronchitis is defined clinically as the presence of a chronic productive cough for 3 months during each of 2 consecutive years (other causes of cough being excluded). Emphysema, on the other hand, is defined pathologically as an abnormal, permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis.

Airflow limitation in emphysema is due to loss of elastic recoil and decrease in airway tethering, whereas chronic bronchitis leads to narrowing of airway caliber and increase in airway resistance. Although some patients predominantly display signs of one of these diseases or the other, most fall somewhere in the middle of the spectrum between the 2 conditions.

Past definitions of COPD have been pessimistic at best, indicating that the disease process is irreversible and that therapy has little to offer. However, a more optimistic view has come to be widely accepted. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines define COPD as a disease state characterized by airflow limitation that is not fully reversible, is usually progressive, and is associated with an abnormal inflammatory response of the lungs to inhaled noxious particles or gases [2].

This GOLD characterization represents a paradigm shift - it suggests that the disease is treatable and preventable.

Oral and inhaled medications are used for patients with stable COPD to reduce dyspnea, improve exercise tolerance, and prevent complications. Most of the medications used in COPD treatment are directed at the potentially reversible mechanisms of airflow limitation.

Pathophysiology. Pathologic changes in COPD occur in the large (central) airways, the small (peripheral) bronchioles, and the lung parenchyma. Most cases of COPD are the result of exposure to noxious stimuli, most often cigarette smoke. The normal inflammatory response is amplified in persons prone to COPD development. The pathogenic mechanisms are not clear but are most likely diverse. Increased numbers of activated polymorphonuclear leukocytes and macrophages release elastases in a manner that cannot be counteracted effectively by antiproteases, resulting in lung destruction.

The primary offender has been found to be human leukocyte elastase, with synergistic roles suggested for proteinase-3 and macrophage-derived matrix metalloproteinases (MMPs), cysteine proteinases, and a plasminogen activator. Additionally, increased oxidative stress caused by free radicals in cigarette smoke, the oxidants released by phagocytes, and polymorphonuclear leukocytes all may lead to apoptosis or necrosis of exposed cells. Accelerated aging and autoimmune mechanisms have also been proposed as having roles in the pathogenesis of COPD [3].

Cigarette smoke causes neutrophil influx, which is required for the secretion of MMPs; this suggests, therefore, that neutrophils and macrophages are required for the development of emphysema.

Studies have also shown that in addition to macrophages, T-lymphocytes, particularly CD8+, play an important role in the pathogenesis of smoking-induced airflow limitation.

To support the inflammation hypothesis further, a stepwise increase in alveolar inflammation has been found in surgical specimens from patients without COPD versus patients with mild or severe emphysema. Indeed, mounting evidence supports the concept that dysregulation of apoptosis and defective clearance of apoptotic cells by macrophages play a prominent role in airway inflammation, particularly in emphysema. Azithromycin has been shown to improve this macrophage clearance function, providing a possible future treatment modality. In patients with stable COPD without known cardiovascular disease, there is a high prevalence of microalbuminuria, which is associated with hypoxemia independent of other risk factors [4].

Etiology

Cigarette smoking. The primary cause of COPD is exposure to tobacco smoke. Overall, tobacco smoking accounts for as much as 90% of COPD risk.

Cigarette smoking induces macrophages to release neutrophil chemotactic factors and elastases, which lead to tissue destruction. Clinically significant COPD develops in 15% of cigarette smokers, although this number is believed to be an underestimate. Age of initiation of smoking, total pack-years, and current smoking status predict COPD mortality.

People who smoke have an increased annual decline in FEV_1: the physiologic normal decline in FEV_1 is estimated to be 20-30 ml/y, but the rate of decline in COPD patients is generally 60 ml/y or greater.

Secondhand smoke, or environmental tobacco smoke, increases the risk of respiratory infections, augments asthma symptoms, and causes a measurable reduction in pulmonary function.

Lung function deviation and lung structural changes are present in people who smoke cigarettes before the clinical signs of airway obstruction reveal them [6]. These changes can be detected by body plethysmography and diffusing capacity measurement with routine spirometry.

Environmental factors. The role of air pollution in the etiology of COPD is unclear; the effect is small when compared with that of cigarette smoking. In developing countries, the use of biomass fuels with indoor cooking and heating is likely to be a major contributor to the worldwide prevalence of COPD. Long-term exposure to traffic-related air pollution may be a factor in COPD in patients with diabetes and asthma [7].

Airway hyperresponsiveness (ie, Dutch hypothesis) stipulates that patients who have nonspecific airway hyperreactivity and who smoke are at increased risk of developing COPD with an accelerated decline in lung function. Nonspecific airway hyperreactivity is inversely related to FEV_1 and may predict a decline in lung function.

The possible role of airway hyperresponsiveness as a risk factor for the development of COPD in people who smoke is unclear. Moreover, bronchial hyperreactivity may result from airway inflammation observed with the development of smoking-related chronic bronchitis. This may contribute to airway remodeling, leading to a more fixed obstruction, as is seen in persons with COPD.

Alpha-1-antitrypsin deficiency (AAT) is a glycoprotein member of the serine protease inhibitor family that is synthesized in the liver and is secreted into the bloodstream. The main purpose of this 394-amino-acid, single-chain protein is to neutralize neutrophil elastase in the lung interstitium and to protect the lung parenchyma from elastolytic breakdown. Severe AAT defiiency predisposes to unopposed elastolysis with the clinical sequela of an early onset of panacinar emphysema.

AAT deficiency is the only known genetic risk factor for developing COPD and accounts for less than 1% of all cases in the US. Severe AAT deficiency leads

to premature emphysema at an average age of 53 years for nonsmokers and 40 years for smokers.

Nearly 24 variants of the AAT molecule have been identified, and all are inherited as codominant alleles. The common M allele (PiM) may be found in 90% of people, and homozygous (PiMM) phenotypes produce serum levels within the reference range. The homozygous PiZZ state is the most common deficiency state and accounts for 95% of people in the severely deficient category.

Intravenous drug use. Emphysema occurs in approximately 2% of persons who use intravenous (IV) drugs. This is attributed to pulmonary vascular damage that results from the insoluble filler (eg, cornstarch, cotton fibers, cellulose, talc) contained in methadone or methylphenidate.

The bullous cysts found in association with IV use of cocaine or heroin occur predominantly in the upper lobes. In contrast, methadone and methylphenidate injections are associated with basilar and panacinar emphysema.

Immunodeficiency syndromes. Human immunodeficiency virus (HIV) infection has been found to be an independent risk factor for COPD, even after controlling for confounding variables such as smoking, IV drug use, race, and age [8].

Apical and cortical bullous lung damage occurs in patients who have autoimmune deficiency syndrome and *Pneumocystis carinii* infection. Reversible pneumatoceles are observed in 10-20% of patients with this infection.

Vasculitis syndrome. Hypocomplementemic vasculitis urticaria syndrome (HVUS) may be associated with COPD. Other manifestations include angioedema, nondeforming arthritis, sinusitis, conjunctivitis, and pericarditis.

Connective tissue disorders. Cutis laxa is a disorder of elastin that is characterized most prominently by the appearance of premature aging. The disease usually is congenital, with various forms of inheritance (ie, dominant, recessive). Precocious emphysema has been described in association with cutis laxa as early as the neonatal period or infancy. The pathogenesis of this disorder includes a defect in the synthesis of elastin or tropoelastin.

Marfan syndrome is an autosomal dominant inherited disease of type I collagen characterized by abnormal length of the extremities, subluxation of the lenses, and cardiovascular abnormality. Pulmonary abnormalities, including emphysema, have been described in approximately 10% of patients.

Ehlers-Danlos syndrome refers to a group of inherited connective tissue disorders with manifestations that include hyperextensibility of the skin and joints, easy bruisability, and pseudotumors; it has also been associated with a higher prevalence of COPD.

Salla disease is an autosomal recessive storage disorder described in Scandinavia; the disease is characterized by intralysosomal accumulation of sialic acid in various tissues. The most important clinical manifestations are severe mental retardation, ataxia, and nystagmus. Precocious emphysema has been described and likely is secondary to impaired inhibitory activity of serum trypsin.

Epidemiology. The National Health Interview Survey reports the prevalence of emphysema at 18 cases per 1000 persons and chronic bronchitis at 34 cases per 1000 persons [9]. While the rate of emphysema has stayed largely unchanged since 2000, the rate of chronic bronchitis has decreased. Another study estimates a prevalence of 10,1% in the US. However, the exact prevalence of COPD in the US is believed to be underestimated. This is largely due to the fact that it is an underdiagnosed (and undertreated) disease, because most patients do not present for medical care until the disease is in a late stage.

The exact prevalence of COPD worldwide is largely unknown, but estimates have varied from 7-19%. The Burden of Obstructive Lung Disease (BOLD) study found a global prevalence of 10,1%. Men were found to have a pooled prevalence of 11,8% and women 8,5%. The numbers vary in different regions of the world. Cape Town, South Africa, has the highest prevalence, affecting 22,2% of men and 16,7% of women.

Hannover, Germany, on the other hand, has the lowest prevalence, of 8,6% for men and 3,7% for women. The differences can be explained in part by site and sex differences in the prevalence of smoking. As noted above, these reports are

widely believed to be underestimates because COPD is known to be underdiagnosed and undertreated. Additionally, the prevalence in women is believed to be increasing.

Although current rates of COPD in men are higher than the rates in women, the rates in women have been increasing. COPD occurs predominantly in individuals older than age 40 years.

Severe, early onset disease likely represents a distinct genotype and is more commonly seen in females, African Americans, and those with a maternal family history of COPD [10].

A study by Mintz et al estimated the prevalence of unidentified COPD [10]. Using the Lung Function Questionnaire (LFQ) and spirometry results, the study determined that approximately 1 in 5 patients (21%) aged 30 years or older with a history of smoking for 10 years or longer seen in a primary care center is likely to have COPD.

Prognosis. COPD is the third leading cause of death in the US [1]. In terms of COPD as the underlying cause of death, absolute mortality rates for US patients aged 25 years or older (2005) were 77,3 deaths per 100000 males and 56,0 deaths per 100000 females, or 64,3 persons per 100000 overall. Internationally, overall mortality rates from COPD vary markedly, from more than 400 deaths per 100000 males aged 65-74 years in Romania to fewer than 100 deaths per 100000 population in Japan.

The FEV_1 was used to predict outcome in COPD until other factors were identified to play a role in determining the outcome of COPD patients. These discoveries resulted in the creation of the multidimensional BODE index (body mass index, obstruction [FEV_1], dyspnea [modified Medical Research Council dyspnea scale], and exercise capacity [6MWD]). This index was developed to assess an individual's risk of death or hospitalization.

Prognosis is based on a point system, with all 4 factors used to determine the score, as follows:

- Body mass index: greater than 21 = 0 points; less than 21 = 1 point,

- FEV $_1$ (postbronchodilator percent predicted): greater than 65% = 0 points; 50-64% = 1 point; 36-49% = 2 points; less than 35% = 3 points,
- Modified Medical Research Council (MMRC) dyspnea scale: MMRC 0 = dyspneic on strenuous exercise (0 points); MMRC 1 = dyspneic on walking a slight hill (0 points); MMRC 2 = dyspneic on walking level ground, must stop occasionally due to breathlessness (1 point); MMRC 3 = dyspneic after walking 100 yards or a few minutes (2 points); MMRC 4 = cannot leave house; dyspneic doing activities of daily living (3 points),
- Six-minute walking distance: greater than 350 meters = 0 points; 250-349 meters = 1 point; 150-249 meters = 2 points; less than 149 meters = 3 points.

The approximate 4-year survival based on the point system above is as follows:

- 0-2 points = 80%
- 3-4 points = 67%
- 5-6 points = 57%
- 7-10 points = 18%

The use of a clinical scoring system reinforces that determinants of prognosis in COPD remain multifactorial. The objective assessments of physical activity, including 6-minute walk test results, are best able to predict mortality. However, additional socioeconomic factors also likely play a role in COPD prognosis; for example, a retrospective cohort study highlighted the increased risk of COPD-related mortality in patients who resides in isolated rural areas [11].

The Clinical COPD Questionnaire (CCQ), which estimates quality of life in patients with COPD, is effective. The CCQ identified that heart disease, depression, and underweight status are independently associated with lower health-related quality of life in patients with COPD.

In a multicenter, prospective, observational study of 201 consecutive patients with moderate-to-severe COPD, Martinez-Garcia et al reported that in addition to smoking, pulmonary hypertension, and declining lung function, all of which are known risk factors for mortality in patients with COPD, bronchiectasis,

which is common in patients with moderate-to-severe COPD, is independently associated with increased risk of all-cause mortality [12].

In this study, those who had bronchiectasis were found to be 2,5 times more likely to die than those who did not. Bronchiectasis remained an independent factor after adjustment for dyspnea, partial pressure of oxygen, body mass index, presence of potentially pathogenic microorganisms in sputum, presence of daily sputum production, number of severe exacerbations and peripheral albumin, and ultrasensitive C-reactive protein concentrations.

Patient Education. It is important to educate the patient with COPD about the disease and to encourage his or her active participation in therapy. The 2 most essential points for the patient to understand are as follows:

- The dangers of smoking and the improvement in quality of life attainable with smoking cessation
- The need to seek medical care early during an exacerbation and to not wait until they are in distress

History. Most patients with COPD seek medical attention late in the course of their disease. Patients often ignore the symptoms because they start gradually and progress over the course of years. Patients often modify their lifestyle to minimize dyspnea and ignore cough and sputum production. With retroactive questioning, a multiyear history can be elicited. Patients typically present with a combination of signs and symptoms of chronic bronchitis, emphysema, and reactive airway disease. These include cough, worsening dyspnea, progressive exercise intolerance, sputum production, and alteration in mental status. Symptoms include the following:

- Productive cough or acute chest illness
- Breathlessness
- Wheezing

Systemic manifestations: decreased fat-free mass, impaired systemic muscle function, osteoporosis, anemia, depression, pulmonary hypertension, cor pulmonale, left-sided heart failure.

A productive cough or an acute chest illness is common. The cough usually is worse in the mornings and produces a small amount of colorless sputum.

Breathlessness is the most significant symptom, but it usually does not occur until the sixth decade of life (although it may occur much earlier). By the time the FEV_1 has fallen to 50% of predicted, the patient is usually breathless upon minimal exertion. In fact, the FEV_1 is the most common variable used to grade the severity of COPD, although it is not the best predictor of mortality.

Wheezing may occur in some patients, particularly during exertion and exacerbations.

Treatment & Management

Approach Considerations. The goal of COPD management is to improve a patient's functional status and quality of life by preserving optimal lung function, improving symptoms, and preventing the recurrence of exacerbations. Currently, no treatments aside from lung transplantation have been shown to significantly improve lung function or decrease mortality. Once the diagnosis of COPD is established, it is important to educate the patient about the disease and to encourage his or her active participation in therapy.

Indications for intensive care admission are confusion, lethargy, respiratory muscle fatigue, worsening hypoxemia, and respiratory acidosis (pH <7,30), as well as clinical concern for impending or active respiratory failure. (BiPAP can be done on the floor in some hospitals, including widely in the United Kingdom).

Approaches to management include recommendations such as those provided by GOLD:

- Stage I (mild obstruction): Reduction of risk factors (influenza vaccine); short-acting bronchodilator as needed
- Stage II (moderate obstruction): Reduction of risk factors (influenza vaccine); short-acting bronchodilator as needed; long-acting bronchodilator(s); cardiopulmonary rehabilitation
- Stage III (severe obstruction): Reduction of risk factors (influenza vaccine); short-acting bronchodilator as needed; long-acting bronchodilator(s);

cardiopulmonary rehabilitation; inhaled glucocorticoids if repeated exacerbations

- Stage IV (very severe obstruction or moderate obstruction with evidence of chronic respiratory failure): Reduction of risk factors (influenza vaccine); short-acting bronchodilator as needed; long-acting bronchodilator(s); cardiopulmonary rehabilitation; inhaled glucocorticoids if repeated exacerbation; long-term oxygen therapy (if criteria met); consider surgical options such as LVRS and lung transplantation

Oral and inhaled medications are used for patients with stable disease to reduce dyspnea and improve exercise tolerance. Most of the medications used are directed at the following 4 potentially reversible causes of airflow limitation in a disease state that has largely fixed obstruction:

- Bronchial smooth muscle contraction
- Bronchial mucosal congestion and edema
- Airway inflammation
- Increased airway secretions

Diet. Inadequate nutritional status associated with low body weight in patients with COPD is associated with impaired pulmonary status, reduced diaphragmatic mass, lower exercise capacity, and higher mortality rates. Nutritional support is an important part of comprehensive care in patients with COPD.

Bronchodilators are the backbone of any COPD treatment regimen. They work by dilating airways, thereby decreasing airflow resistance. This increases airflow and decreases dynamic hyperinflation. Lack of response in pulmonary function testing should not preclude their use. These drugs provide symptomatic relief but do not alter disease progression or decrease mortality.

Beta-2 agonists and anticholinergics. The initial choice of agent remains in debate. Historically, beta-2 agonists were considered first line and anticholinergics were added as adjuncts. Not surprisingly, studies have shown combination therapy results in greater bronchodilator response and provides greater relief. Monotherapy

with either agent or combination therapy with both are acceptable options. The adverse effect profile may help guide therapy. Generally, long-acting bronchodilators are more beneficial than short-acting ones [5].

Tiotropium did show a significant reduction in the frequency of COPD exacerbations and hospitalizations and an improvement in quality of life [13].

Phosphodiesterase inhibitors increase intracellular cyclic adenosine monophosphate (cAMP) and result in bronchodilation. Additionally, they may improve diaphragm muscle contractility and stimulate the respiratory center.

Endogenous opioids modulated the intensity and unpleasantness of breathlessness in patients with COPD.

Beta-adrenergic antagonists (beta-blockers). Cardiovascular disease is common in patients with COPD and is a leading cause of mortality; however, use of beta-blockers has been discouraged in these patients due to a perceived risk of bronchospasm and concern about inhibition of beta-agonist medication. However, the addition of a cardioselective beta-blocker to established inhaled treatment did not appear to harm pulmonary function and did reduce COPD exacerbations, hospital admissions, and all cause mortality versus controls over a mean follow-up of 4,35 years [14].

Smoking cessation continues to be the most important therapeutic intervention for COPD. Most patients with COPD have a history of smoking or are currently smoking tobacco products. A smoking cessation plan is an essential part of a comprehensive management plan.

However, the success rates for cessation programs are low because of the addictive power of nicotine. These rates can also be negatively impacted by such factors as conditioned responses to smoking-associated stimuli, poor education, forceful promotional campaigns by the tobacco industry, and psychological problems, including depression. The process of smoking cessation typically requires multiple interventional approaches, including both pharmacologic and non-pharmacologic modalities, and will likely require multiple attempts to maintain success.

The transition from smoking to not smoking occurs in the following 5 stages:

- Precontemplation
- Contemplation
- Preparation
- Action
- Maintenance

Smoking intervention programs include self-help, group, health care provider delivered, workplace, and community programs.

Setting a quit date may be helpful. Physicians and other health care providers should participate in setting the target date and follow-up with respect to maintenance.

Successful cessation programs usually use the following resources and tools:

- Patient education
- A target date to quit
- Follow-up support
- Relapse prevention
- Advice for healthy lifestyle changes
- Social support systems
- Adjuncts to treatment (ie, pharmacologic agents).

The intensive behavioral interventions, including (but not limited to) individual counseling and telephone counseling, offer considerable benefit for increasing smoking abstinence.

According to the US Preventive Services Task Force (USPSTF) guidelines on preventing tobacco use and tobacco-caused disease, clinicians should ask all adult patients about their use of tobacco products and provide cessation interventions to current users [15]. The guideline engages a «5-A» approach to counseling that includes the following:

- Ask about tobacco use
- Advise to quit through personalized messages
- Assess willingness to quit

- Assist with quitting
- Arrange follow-up care and support

Brief behavioral counseling (<10 min) and pharmacotherapy are each effective alone - although they are most effective when used together. The USPSTF also advises clinicians to ask all pregnant women, regardless of age, about tobacco use. Those who currently smoke should receive pregnancy-tailored counseling supplemented with self-help materials.

Supervised use of pharmacologic agents is an important adjunct to self-help and group smoking cessation programs.

Nicotine is the ingredient in cigarettes primarily responsible for tobacco addiction. Withdrawal from nicotine may cause unpleasant adverse effects, including anxiety, irritability, difficulty concentrating, anger, fatigue, drowsiness, depression, and sleep disruption. These effects usually occur during the first several weeks.

Nicotine replacement therapies after smoking cessation reduce withdrawal symptoms. If a smoker requires his/her first cigarette within 30 minutes of waking, the individual most likely is highly addicted and would benefit from nicotine replacement therapy.

Several nicotine replacement therapies are available.

Nicotine polacrilex (Nicorette, Nicorette Plus) is a chewing gum and has better quit rates than does counseling alone. Nicotine replacement therapy chewing pieces are marketed in 2 strengths (2 mg, 4 mg). An individual who smokes 1 pack per day should use 4-mg pieces. The 2-mg pieces are to be used by individuals who smoke less than 1 pack per day. Instruct patients to chew hourly and also to chew when needed for their initial cravings for 2 weeks. Gradually reduce the amount chewed over the next 3 months.

Transdermal nicotine patches are readily available for replacement therapy. Long-term success rates are 22-42%, compared with 2-25% for placebo. These agents are well tolerated, and the adverse effects are limited to local skin reactions.

Each of these products is dosed with a scheduled graduated decrease in nicotine over 6-10 weeks.

The use of the antidepressant bupropion is also effective for smoking cessation. This non-nicotine aid to smoking cessation enhances central nervous system nonadrenergic function. One study demonstrated that 23% of patients sustained cessation at 1 year, compared with 12% who sustained cessation with the placebo. Bupropion may also be effective in patients who have not been able to quit smoking with nicotine replacement therapy.

Another drug used in smoking cessation is varenicline (a partial agonist selective for alpha-4, beta-2 nicotinic acetylcholine receptors). Its action is thought to result from activity at a nicotinic receptor subtype, where its binding produces agonist activity while simultaneously preventing nicotine binding. Agonistic activity is significantly lower than nicotine.

Prevention of Acute COPD Exacerbations

In 2015, the American College of Chest Physicians and Canadian Thoracic Society released guidelines on the prevention of acute exacerbations of COPD [16]. Major recommendations include the following:

- The 23-valent pneumococcal vaccine is recommended. However, evidence is insufficient that pneumococcal vaccination prevents COPD acute exacerbations.
- Administer the influenza vaccine annually.
- Provide smoking cessation counseling and treatment.
- Provide pulmonary rehabilitation for those with moderate, severe, or very severe COPD who have had a recent exacerbation.
- Provide education with a written action plan and case management.
- For patients with a history of COPD acute exacerbations, education and case management should include direct access to a healthcare specialist at least monthly.
- Telemonitoring is not beneficial compared with usual care.
- In patients with moderate to severe COPD:

- Long-acting beta-2 agonists are beneficial, but long-acting muscarinic antagonists are superior to prevent moderate to severe acute exacerbations.
- Use a short-acting muscarinic antagonist rather than a short-acting beta-2 agonist as monotherapy to prevent acute mild-to-moderate exacerbations.
- Use a short-acting muscarinic antagonist plus a short-acting beta-2 agonist to prevent acute moderate exacerbations of COPD.
- Use a long-acting beta-2 agonist monotherapy rather than a short-acting muscarinic antagonist monotherapy to prevent acute exacerbations of COPD.
- Use a long-acting muscarinic antagonist instead of a short-acting muscarinic antagonist to prevent acute moderate-to-severe exacerbations.
- A combination of short-acting muscarinic antagonist plus a long-acting beta-2 agonist is better than long-acting beta-2 agonist monotherapy to prevent acute mild-to-moderate exacerbations.

- In patients with stable, moderate severe, and very severe COPD:
  - A maintenance combination of inhaled corticosteroid and long-acting beta-2 agonist therapy is better than corticosteroid monotherapy or beta-2 agonist monotherapy to prevent acute exacerbations of COPD.
- In patients with stable COPD:
  - Use a maintenance combination of inhaled corticosteroid and long-acting beta-2 agonist therapy or inhaled long-acting anticholinergic monotherapy for acute exacerbations.
  - A maintenance combination of inhaled long-acting anticholinergic, corticosteroid, and long-acting beta-2 agonist therapy or inhaled long-acting anticholinergic monotherapy are both effective to prevent acute exacerbations.
- In patients aged 40 years who are smokers or have a history of smoking:

- Use a long-term macrolide to prevent acute exacerbations in patients with moderate-to-severe COPD with a history of one or more moderate or severe exacerbations in the prior year despite optimal maintenance inhaler therapy.
- In patients with an acute exacerbation, systemic corticosteroids should be given orally or intravenously to prevent hospitalization for subsequent acute exacerbations of COPD in the first 30 days (only) after initial exacerbation.
- For patients with moderate-to-severe COPD and chronic bronchitis and a history of at least one exacerbation in the last year, use roflumilast to prevent acute exacerbations.
- For stable patients, use an oral slow-release theophylline twice daily to prevent acute exacerbations.
- For patients with moderate-to-severe COPD and 2 or more exacerbations in the last 2 years, use oral N-acetylcysteine to prevent acute exacerbations.
- For stable patients who continue to have acute exacerbations in spite of maximal therapy to reduce them, oral carbocysteine should be used to prevent acute exacerbations if available.
- For those with moderate-to-severe COPD at risk for exacerbations, statins are not recommended to prevent exacerbations.

Vaccination to Reduce Infections. Infections can lead to COPD exacerbations. Vaccinations are a safe and effective modality to reduce infections in susceptible COPD patients. The pneumococcal vaccine should be offered to all patients older than 65 years or to patients of any age who have an FEV_1 of less than 40% of predicted. The influenza vaccine should be given annually to all COPD patients.

Alpha-1-Antitrypsin Deficiency Treatment involves reducing the neutrophil elastase burden, primarily by smoking cessation, and augmenting the levels of AAT. Available augmentation strategies include pharmacologic attempts

to increase endogenous production of AAT by the liver (ie, danazol, tamoxifen) and administration of purified AAT by periodic intravenous infusion or by inhalation. Tamoxifen can increase endogenous production of AAT to a limited extent, so this may be beneficial in persons with the PISZ phenotype.

Intravenous AAT augmentation therapy is the only available approach that can increase serum levels to greater than 11 mmol/L, the protective threshold. Studies show that the infusions can maintain levels of more than 11 mmol/L, and replacement is administered weekly (60 mg/kg), biweekly (120 mg/kg), or monthly (250 mg/kg).

Purified AAT is currently available in 3 formulations, with trade names of Prolastin, Zemaira, and Aralast, all of which are derived from donor blood. Synthetic formulations of AAT are under development but not yet available. The ability of intravenous AAT augmentation to alter the clinical course of patients with AAT deficiency has not been demonstrated. Uncontrolled observations of patients suggest that the FEV_1 may fall at a slower rate in patients who receive AAT replacement [17].

Long-term Monitoring. Follow-up. Disposition after an AECOPD depends on the clinical picture for each patient more than on any single laboratory value or test. In general, the longer the exacerbation, the more airway edema and debris are present. Nearly all discharged patients should receive a short steroid burst and an increase in the frequency of inhaler therapy. Close follow-up should be arranged with the patient's regular care provider. Other therapies should be considered on a case-by-case basis.

Additional follow-up recommendations are as follows:

- Patients with severe or unstable disease should be seen monthly
- When their condition is stable, patients may be seen biannually
- Check theophylline level with each dose adjustment, when interacting medications are added, and routinely every 6-12 months
- For patients on home oxygen, check arterial blood gases (ABGs) yearly or with any change in condition

- Monitor oxygen saturation more frequently than ABGs

Pulmonary rehabilitation. Many patients with COPD are unable to enjoy life to the fullest because of shortness of breath, physical limitations, and inactivity. Pulmonary rehabilitation encompasses an array of therapeutic modalities designed to improve the patient's quality of life by decreasing airflow limitation, preventing secondary medical complications, and alleviating respiratory symptoms. The 3 major goals of the comprehensive management of COPD are the following:

- Lessen airflow limitation
- Prevent and treat secondary medical complications (eg, hypoxemia, infection)
- Decrease respiratory symptoms and improve quality of life

Successful implementation of a pulmonary rehabilitation program usually requires a team approach, with individual components provided by healthcare professionals who have experience in managing COPD (eg, physician, dietitian, nurse, respiratory therapist, exercise physiologist, physical therapist, occupational therapist, recreational therapist, cardiorespiratory technician, pharmacist, psychosocial professionals). This multidisciplinary approach emphasizes the following:

- Patient and family education
- Smoking cessation
- Medical management (including oxygen and immunization)
- Respiratory and chest physiotherapy
- Physical therapy with bronchopulmonary hygiene, exercise, and vocational rehabilitation
- Psychosocial support

As a result of rehabilitation, improvements have been shown in objective measures of patients’ quality of life, well-being, and health status, including reduction in respiratory symptoms, increases in exercise tolerance and functional

activities (eg, walking), reduction in anxiety and depression, and increases in feelings of control and self-esteem.

An observational study has shown that pulmonary rehabilitation also improves the BODE index score in patients with COPD and is associated with better outcomes. Quality of life improvements after pulmonary rehabilitation can also be measured using the COPD Assessment Test (CAT), an 8-question patient-completed instrument [18]. In addition, pulmonary rehabilitation results in substantial savings in health care costs by reducing hospitalizations and the use of medical resources.

Pulmonary rehabilitation programs usually are conducted in an outpatient setting. A rehabilitation program may include a number of components and should be tailored to the needs of the individual patient. Provide all patients who complete the program with guidelines for continuing at home.

Education is a key to comprehensive pulmonary rehabilitation. The educational component prepares the patient and family to be actively involved in providing care. This reliance on patients to assume charge of their care is known as collaborative self-management.

Exercise training is a mandatory component of pulmonary rehabilitation. Patients with COPD should perform aerobic lower extremity endurance exercises regularly to enhance performance of daily activities and reduce dyspnea. Upper extremity exercise training improves dyspnea and allows increased activities of daily living requiring the use of upper extremities.

Breathing retraining techniques (eg, diaphragmatic, pursed lip breathing) may improve the ventilatory pattern and prevent dynamic airway compression.

Special concerns. Many commercial airplanes fly at altitudes of 30000-40000 feet. However, the cabin is pressurized to an altitude of 5000-8000 feet. At these altitudes, atmospheric partial pressure of oxygen (PO_2) is 132-109 mm Hg, compared with 159 mm Hg at sea level.

Acute reduction in PO_2 stimulates peripheral chemoreceptors, which results in hyperventilation. When determining whether or not a COPD patient can safely

fly, the clinician should first use a prediction equation to determine whether the patient will become hypoxemic at high altitudes. A prediction equation used to estimate PaO_2 at 8000 feet (2440 m) is as follows:

$$PaO_2 = 22,8 – 2,74X + 0,68Y$$

(X = altitude; Y = arterial PO_2 at sea level)

A predicted PaO_2 of 50 mm Hg or less at an altitude of 8000 feet is an indication for supplemental oxygen. Arrange supplemental oxygen prior to the flight directly through the airline or through the airline agent (at an extra expense). If there is any question regarding the calculation, many pulmonary physiology labs can also perform altitude simulation tests to confirm or refute the need for in-flight oxygen.

Patients with COPD may develop substantial decreases in nocturnal PaO_2 during all phases of sleep, but particularly during the rapid eye movement phase. These episodes are associated initially with a rise in pulmonary arterial pressures and a disturbance in sleep architecture, but they may develop into pulmonary arterial hypertension and cor pulmonale if hypoxemia remains untreated.

Prescribe oxygen for patients who have daytime PaO_2 greater than 60 mm Hg but who demonstrate substantial nocturnal hypoxemia.

End-of-Life Care. COPD is a chronic disease that is preventable and treatable but largely incurable. Given the progressive nature of the disease, as well as the morbidity and mortality associated with it, clinicians should always include end-of-life care discussions in their visits with patients. These discussions should focus on palliative efforts to improve quality of life, as well as assistance with advanced directives, advanced care planning, and referrals for hospice and home care when needed.

Medication Summary. Oral and inhaled medications are used for patients with stable COPD to reduce dyspnea, improve exercise tolerance, and prevent complications. Most of the medications used in COPD treatment are directed at the following 4 potentially reversible mechanisms of airflow limitation:

- Bronchial smooth muscle contraction

- Bronchial mucosal congestion and edema
- Airway inflammation
- Increased airway secretions.

Bronchodilators act to decrease muscle tone in small and large airways in the lungs, thereby increasing ventilation. The category includes subcutaneous medications, beta-adrenergics, methylxanthines, and anticholinergics.

Additionally, opioids have been shown in multiple studies to relieve dyspnea, particularly near the end of life. Dosage is very patient specific. Currow et al used a low, once-daily dose of sustained-release morphine for chronic refractory dyspnea [19].

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ASTHMA

Background. Asthma is a common chronic disease worldwide and affects approximately 26 million persons in the US. It is the most common chronic disease in childhood, affecting an estimated 7 million children, and it is a common cause of hospitalization for children in the US.

Anatomy. The airways of the lungs consist of the cartilaginous bronchi, membranous bronchi, and gas-exchanging bronchi termed the respiratory bronchioles and alveolar ducts. While the first 2 types function mostly as anatomic dead space, they also contribute to airway resistance. The smallest non-gas-exchanging airways, the terminal bronchioles, are approximately 0.5 mm in diameter; airways are considered small if they are less than 2 mm in diameter [1].

Airway structure consists of the following:

- Mucosa, which is composed of epithelial cells that are capable of specialized mucous production and a transport apparatus
- Basement membrane
- A smooth-muscle matrix extending to the alveolar entrances
- Predominantly fibrocartilaginous or fibroelastic-supporting connective tissue.

Cellular elements include mast cells, which are involved in the complex control of releasing histamine and other mediators. Basophils, eosinophils, neutrophils, and macrophages also are responsible for extensive mediator release in the early and late stages of bronchial asthma. Stretch and irritant receptors reside in the airways, as do cholinergic motor nerves, which innervate the smooth muscle and glandular units. In bronchial asthma, smooth muscle contraction in an airway is greater than that expected for its size if it were functioning normally, and this contraction varies in its distribution.

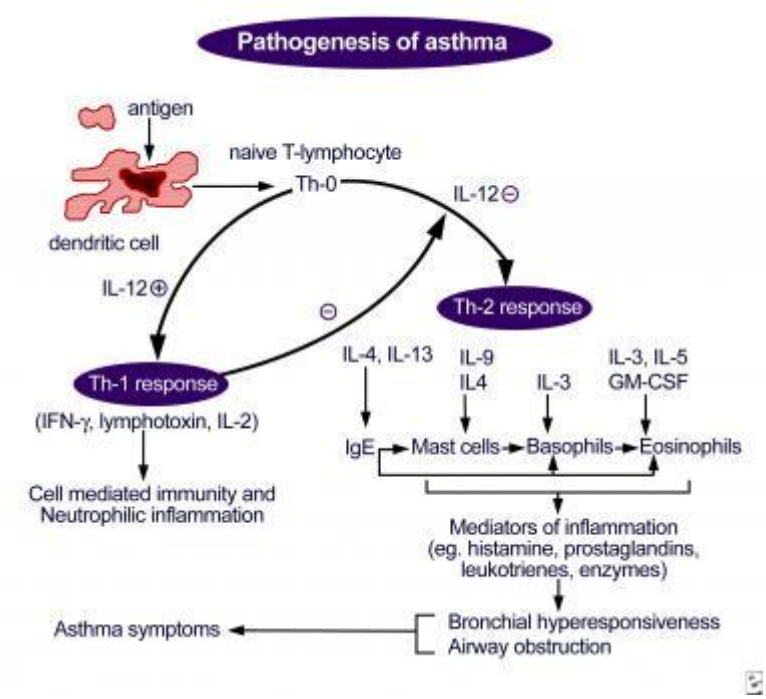
Pathophysiology. The 2007 Expert Panel Report 3 (EPR-3) of the National Asthma Education and Prevention Program (NAEPP) noted several key changes in the understanding of the pathophysiology of asthma [1]:

- The critical role of inflammation has been further substantiated, but evidence is emerging for considerable variability in the pattern of inflammation, thus indicating phenotypic differences that may influence treatment responses
- Of the environmental factors, allergic reactions remain important. Evidence also suggests a key and expanding role for viral respiratory infections in these processes
- The onset of asthma for most patients begins early in life, with the pattern of disease persistence determined by early, recognizable risk factors including atopic disease, recurrent wheezing, and a parental history of asthma
- Current asthma treatment with anti-inflammatory therapy does not appear to prevent progression of the underlying disease severity

The pathophysiology of asthma is complex and involves the following components:

- Airway inflammation
- Intermittent airflow obstruction
- Bronchial hyperresponsiveness

Airway inflammation. The mechanism of inflammation in asthma may be acute, subacute, or chronic, and the presence of airway edema and mucus secretion also contributes to airflow obstruction and bronchial reactivity. Varying degrees of mononuclear cell and eosinophil infiltration, mucus hypersecretion, desquamation of the epithelium, smooth muscle hyperplasia, and airway remodeling are present [2]. See the image below.



Pathogenesis of asthma.Antigen presentation by the dendritic cell with the lymphocyte and cytokine response leading to airway inflammation and asthma symptoms [2].

Some of the principal cells identified in airway inflammation include mast cells, eosinophils, epithelial cells, macrophages, and activated T-lymphocytes. T-lymphocytes play an important role in the regulation of airway inflammation through the release of numerous cytokines. Other constituent airway cells, such as fibroblasts, endothelial cells, and epithelial cells, contribute to the chronicity of the disease. Other factors, such as adhesion molecules (eg, selectins, integrins), are critical in directing the inflammatory changes in the airway. Finally, cell-derived mediators influence smooth muscle tone and produce structural changes and remodeling of the airway.

The presence of airway hyperresponsiveness or bronchial hyperreactivity in asthma is an exaggerated response to numerous exogenous and endogenous stimuli. The mechanisms involved include direct stimulation of airway smooth muscle and indirect stimulation by pharmacologically active substances from mediator-secreting cells such as mast cells or nonmyelinated sensory neurons. The

degree of airway hyperresponsiveness generally correlates with the clinical severity of asthma.

A greater proportion of chymase-positive mast cells in the airways and increased prostaglandin D2 levels were identified as important predictors of severe asthma as compared with other steroid-treated subjects with asthma [3].

Chronic inflammation of the airways is associated with increased bronchial hyperresponsiveness, which leads to bronchospasm and typical symptoms of wheezing, shortness of breath, and coughing after exposure to allergens, environmental irritants, viruses, cold air, or exercise. In some patients with chronic asthma, airflow limitation may be only partially reversible because of airway remodeling (hypertrophy and hyperplasia of smooth muscle, angiogenesis, and subepithelial fibrosis) that occurs with chronic untreated disease.

Airway inflammation in asthma may represent a loss of normal balance between two "opposing" populations of Th lymphocytes. Two types of Th lymphocytes have been characterized: Th1 and Th2. Th1 cells produce interleukin (IL)-2 and IFN-α, which are critical in cellular defense mechanisms in response to infection. Th2, in contrast, generates a family of cytokines (IL-4, IL-5, IL-6, IL-9, and IL-13) that can mediate allergic inflammation.

The current "hygiene hypothesis" of asthma illustrates how this cytokine imbalance may explain some of the dramatic increases in asthma prevalence in westernized countries. This hypothesis is based on the concept that the immune system of the newborn is skewed toward Th2 cytokine generation (mediators of allergic inflammation). Following birth, environmental stimuli such as infections activate Th1 responses and bring the Th1/Th2 relationship to an appropriate balance. However, unequivocal support for the "hygiene hypothesis" has not been demonstrated [4].

Airflow obstruction can be caused by a variety of changes, including acute bronchoconstriction, airway edema, chronic mucous plug formation, and airway remodeling. Acute bronchoconstriction is the consequence of immunoglobulin E-dependent mediator release upon exposure to aeroallergens and is the primary

component of the early asthmatic response. Airway edema occurs 6-24 hours following an allergen challenge and is referred to as the late asthmatic response. Chronic mucous plug formation consists of an exudate of serum proteins and cell debris that may take weeks to resolve. Airway remodeling is associated with structural changes due to long-standing inflammation and may profoundly affect the extent of reversibility of airway obstruction.

Airway obstruction causes increased resistance to airflow and decreased expiratory flow rates. These changes lead to a decreased ability to expel air and may result in hyperinflation. The resulting overdistention helps maintain airway patency, thereby improving expiratory flow; however, it also alters pulmonary mechanics and increases the work of breathing.

Bronchial hyperresponsiveness. Hyperinflation compensates for the airflow obstruction, but this compensation is limited when the tidal volume approaches the volume of the pulmonary dead space; the result is alveolar hypoventilation. Uneven changes in airflow resistance, the resulting uneven distribution of air, and alterations in circulation from increased intra-alveolar pressure due to hyperinflation all lead to ventilation-perfusion mismatch. Vasoconstriction due to alveolar hypoxia also contributes to this mismatch. Vasoconstriction is also considered an adaptive response to ventilation/perfusion mismatch.

In the early stages, when ventilation-perfusion mismatch results in hypoxia, hypercarbia is prevented by the ready diffusion of carbon dioxide across alveolar capillary membranes. Thus, patients with asthma who are in the early stages of an acute episode have hypoxemia in the absence of carbon dioxide retention. Hyperventilation triggered by the hypoxic drive also causes a decrease in $PaCO_2$. An increase in alveolar ventilation in the early stages of an acute exacerbation prevents hypercarbia. With worsening obstruction and increasing ventilation-perfusion mismatch, carbon dioxide retention occurs. In the early stages of an acute episode, respiratory alkalosis results from hyperventilation. Later, the increased work of breathing, increased oxygen consumption, and increased cardiac

output result in metabolic acidosis. Respiratory failure leads to respiratory acidosis due to retention of carbon dioxide as alveolar ventilation decreases.

Etiology

Factors that can contribute to asthma or airway hyperreactivity may include any of the following:

- Environmental allergens (eg, house dust mites; animal allergens, especially cat and dog; cockroach allergens; and fungi)
- Viral respiratory tract infections
- Exercise, hyperventilation
- Gastroesophageal reflux disease
- Chronic sinusitis or rhinitis
- Aspirin or nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity, sulfite sensitivity
- Use of beta-adrenergic receptor blockers (including ophthalmic preparations)
- Obesity
- Environmental pollutants, tobacco smoke
- Occupational exposure
- Irritants (eg, household sprays, paint fumes)
- Various high- and low-molecular-weight compounds (eg, insects, plants, latex, gums, diisocyanates, anhydrides, wood dust, and fluxes; associated with occupational asthma)
- Emotional factors or stress
- Perinatal factors (prematurity and increased maternal age; maternal smoking and prenatal exposure to tobacco smoke; breastfeeding has not been definitely shown to be protective)

Aspirin-induced asthma. The triad of asthma, aspirin sensitivity, and nasal polyps affects 5-10% of patients with asthma. Most patients experience symptoms during the third to fourth decade. A single dose can provoke an acute asthma exacerbation, accompanied by rhinorrhea, conjunctival irritation, and flushing of

the head and neck. It can also occur with other nonsteroidal anti-inflammatory drugs and is caused by an increase in eosinophils and cysteinyl leukotrienes after exposure [1].

Gastroesophageal reflux disease. The presence of acid in the distal esophagus, mediated via vagal or other neural reflexes, can significantly increase airway resistance and airway reactivity. Patients with asthma are 3 times more likely to also have GERD [5]. Some people with asthma have significant gastroesophageal reflux without esophageal symptoms. Gastroesophageal reflux was found to be a definite asthma-causing factor (defined by a favorable asthma response to medical antireflux therapy) in 64% of patients; clinically silent reflux was present in 24% of all patients [5].

Work-related asthma. Occupational factors are associated with 10-15% of adult asthma cases. More than 300 specific occupational agents have been associated with asthma. High-risk jobs include farming, painting, janitorial work, and plastics manufacturing. Given the prevalence of work-related asthma, the American College of Chest Physicians (ACCP) supports consideration of work-related asthma in all patients presenting with new-onset or worsening asthma. An ACCP consensus statement defines work-related asthmas as including occupational asthma (ie, asthma induced by sensitizer or irritant work exposures) and work-exacerbated asthma (ie, preexisting or concurrent asthma worsened by work factors) [6].

Two types of occupational asthma are recognized: immune-related and non-immune-related. Immune-mediated asthma has a latency of months to years after exposure. Non-immune-mediated asthma, or irritant-induced asthma (reactive airway dysfunction syndrome), has no latency period and may occur within 24 hours after an accidental exposure to high concentrations of respiratory irritants. Pay careful attention to the patient's occupational history. Those with a history of asthma who report worsening of symptoms during the week and improvement during the weekends should be evaluated for occupational exposure. Peak-flow monitoring during work (optimally, at least 4 times a day) for at least 2 weeks and

a similar period away from work is one recommended method to establish the diagnosis [6].

Viral exposure in children. Evidence suggests that rhinovirus illness during infancy is a significant risk factor for the development of wheezing in preschool children and a frequent trigger of wheezing illnesses in children with asthma. [16] Human rhinovirus (HRV) C is a newly identified genotype of HRV found in patients with respiratory tract infections. The presence of HRVC is ssociated with more severe asthma.

Approximately 80-85% of childhood asthma episodes are associated with prior viral exposure. Prior childhood pneumonia due to infection by respiratory syncytial virus, *Mycoplasma pneumoniae,* and/or *Chlamydia* species was found in more than 50% of a small sample of children aged 7-9 years who later had asthma []. [18] Treatment with antibiotics appropriate for these organisms improves the clinical signs and symptoms of asthma.

Sinusitis. Of patients with asthma, 50% have concurrent sinus disease. Sinusitis is the most important exacerbating factor for asthma symptoms. Either acute infectious sinus disease or chronic inflammation may contribute to worsening airway symptoms. Treatment of nasal and sinus inflammation reduces airway reactivity. Treatment of acute sinusitis requires at least 10 days of antibiotics to improve asthma symptoms.

Exercise-induced asthma (EIA), or exercise-induced bronchoconstriction (EIB), is an asthma variant defined as a condition in which exercise or vigorous physical activity triggers acute bronchoconstriction in persons with heightened airway reactivity. It is observed primarily in persons who have asthma (exercise-induced bronchoconstriction in asthmatic persons) but can also be found in patients with normal resting spirometry findings with atopy, aller gic rhinitis, or cystic fibrosis and even in healthy persons, many of whom are elite or cold weather athletes (exercise-induced bronchoconstriction in athletes).

The pathogenesis of exercise-induced bronchoconstriction is controversial. The disease may be mediated by water loss from the airway, heat loss from the

airway, or a combination of both. The upper airway is designed to keep inspired air at 100% humidity and body temperature at 37°C (98.6°F). The nose is unable to condition the increased amount of air required for exercise, particularly in athletes who breathe through their mouths. The abnormal heat and water fluxes in the bronchial tree result in bronchoconstriction, occurring within minutes of completing exercise. Results from bronchoalveolar lavage studies have not demonstrated an increase in inflammatory mediators. These patients generally develop a refractory period, during which a second exercise challenge does not cause a significant degree of bronchoconstriction.

Factors that contribute to exercise-induced bronchoconstriction symptoms (in both persons with asthma and athletes) include the following:

- Exposure to cold or dry air
- Environmental pollutants (eg, sulfur, ozone)
- Level of bronchial hyperreactivity
- Chronicity of asthma and symptomatic control
- Duration and intensity of exercise
- Allergen exposure in atopic individuals
- Coexisting respiratory infection

The assessment and diagnosis of exercise-induced bronchoconstriction is made more often in children and young adults than in older adults and is related to high levels of physical activity. Exercise-induced bronchoconstriction can be observed in persons of any age based on the level of underlying airway reactivity and the level of physical exertion.

Genetics. Polymorphisms in the gene that encodes platelet-activating factor hydrolase, an intrinsic neutralizing agent of platelet-activating factor in most humans, may play a role in susceptibility to asthma and asthma severity [8].

The prevalence of asthma is reduced in association with certain infections (*Mycobacterium tuberculosis*, measles, or hepatitis A); rural living; exposure to other children (eg, presence of older siblings and early enrollment in childcare); and less frequent use of antibiotics. Furthermore, the absence of these lifestyle

events is associated with the persistence of a Th2 cytokine pattern. Under these conditions, the genetic background of the child, with a cytokine imbalance toward Th2, sets the stage to promote the production of immunoglobulin E (IgE) antibody to key environmental antigens (eg, dust mites, cockroaches, *Alternaria,* and possibly cats). Therefore, a gene-by-environment interaction occurs in which the susceptible host is exposed to environmental factors that are capable of generating IgE, and sensitization occurs.

A reciprocal interaction is apparent between the 2 subpopulations, in which Th1 cytokines can inhibit Th2 generation and vice versa. Allergic inflammation may be the result of an excessive expression of Th2 cytokines. Alternatively, the loss of normal immune balance arises from a cytokine dysregulation in which Th1 activity in asthma is diminished [8].

Obesity. There was explored the relationship between asthma, obesity, and abnormal lipid and glucose metabolism [9]. The study found that community-based data linked asthma, body mass, and metabolic variables in children. Evidence is accumulating that individuals with a high body mass index have worse asthma control and sustained weight loss improves asthma control [9]. Accelerated weight gain in early infancy is associated with increased risks of asthma symptoms according to one study of preschool children.

Epidemiology. Asthma affects 5-10% of the population or an estimated 23.4 million persons, including 7 million children [6]. The overall prevalence rate of exercise-induced bronchospasm is 3-10% of the general population if persons who do not have asthma or allergy are excluded, but the rate increases to 12-15% of the general population if patients with underlying asthma are included. Asthma affects an estimated 300 million individuals worldwide. Annually, the World Health Organization (WHO) has estimated that 15 million disability-adjusted life-years are lost and 250 000 asthma deaths are reported worldwide [10].

In the US, asthma prevalence, especially morbidity and mortality, is higher in blacks than in whites. Although genetic factors are of major importance in

determining a predisposition to the development of asthma, environmental factors play a greater role than racial factors in asthma onset.

Asthma is common in industrialized nations such as Canada, England, Australia, Germany, and New Zealand, where much of the asthma data have been collected. The prevalence rate of severe asthma in industrialized countries ranges from 2-10%. Trends suggest an increase in both the prevalence and morbidity of asthma, especially in children younger than 6 years. Factors that have been implicated include urbanization, air pollution, passive smoking, and change in exposure to environmental allergens.

Asthma predominantly occurs in boys in childhood, with a male-to-female ratio of 2:1 until puberty, when the male-to-female ratio becomes 1:1. Asthma prevalence is greater in females after puberty, and the majority of adult-onset cases diagnosed in persons older than 40 years occur in females. Boys are more likely than girls to experience a decrease in symptoms by late adolescence.

Asthma prevalence is increased in very young persons and very old persons because of airway responsiveness and lower levels of lung function. Two thirds of all asthma cases are diagnosed before the patient is aged 18 years. Approximately half of all children diagnosed with asthma have a decrease or disappearance of symptoms by early adulthood [10].

Prognosis. International asthma mortality is reported as high as 0.86 deaths per 100000 persons in some countries. US asthma mortality rates in 2009 were reported at 1 death per 100000 persons. Mortality is primarily related to lung function, with an 8-fold increase in patients in the lowest quartile, but mortality has also been linked with asthma management failure, especially in young persons. Other factors that impact mortality include age older than 40 years, cigarette smoking more than 20 pack-years, blood eosinophilia, forced expiratory volume in one second (FEV_1) of 40-69% predicted, and greater reversibility [10].

The estimate of lost work and school time from asthma is approximately 100 million days of restricted activity. Approximately 500000 annual hospitalizations (40.6% in individuals aged 18 y or younger) are due to asthma. Each year, an

estimated 1.7 million people (47.8% of them aged 18 years or younger) require treatment in an emergency department. For 2010, the annual expenditures for health and lost productivity due to asthma was projected to be $20.7 billion [11].

Nearly one half of children diagnosed with asthma will have a decrease in symptoms and require less treatment by late adolescence or early adulthood. In a study of 900 children with asthma, 6% required no treatment after 1 year, and 39% only required intermittent treatment.

Patients with poorly controlled asthma develop long-term changes over time (i.e., with airway remodeling). This can lead to chronic symptoms and a significant irreversible component to their disease. Many patients who develop asthma at an older age also tend to have chronic symptoms.

Patient Education

The need for patient education about asthma and the establishment of a partnership between patient and clinician in the management of the disease was emphasized by EPR-3 [1].

The key points of education include the following:

- Patient education should be integrated into every aspect of asthma care
- All members of the healthcare team, including nurses, pharmacists, and respiratory therapists, should provide education.
- Clinicians should teach patients asthma self-management based on basic asthma facts, self-monitoring techniques, the role of medications, inhaler use, and environmental control measures.
- Treatment goals should be developed for the patient and family.
- A written, individualized, daily self-management plan should be developed.
- Several well-validated asthma action plans are now available and are key in the management of asthma and should therefore be reviewed: ACT (Asthma Control Test), ATAQ (Asthma Therapy Assessment Questionnaire), and ACQ (Asthma Control Questionnaire) [12].

School-based asthma education programs improved knowledge of asthma, self-efficacy, and self-management behaviors in children aged 4-17 years, but the

programs had less effect on quality of life, days of symptoms, nights with symptoms, and school absences [12].

History. A detailed assessment of the medical history should address the following:

- Whether symptoms are attributable to asthma
- Whether findings support the likelihood of asthma (eg, family history)
- Asthma severity
- Identification of possible precipitating factors

Family history may be pertinent for asthma, allergy, sinusitis, rhinitis, eczema, and nasal polyps. The social history may include home characteristics, smoking, workplace or school characteristics, educational level, employment, social support, factors that may contribute to nonadherence of asthma medications, and illicit drug use.

The patient's exacerbation history is important with respect to the following:

- Usual prodromal signs or symptoms
- Rapidity of onset
- Associated illnesses
- Number in the last year
- Need for emergency department visits, hospitalizations, ICU admissions, intubations
- Missed days from work or school or activity limitation

The patient's perception of his or her asthma is important regarding knowledge of asthma and treatment, use of medications, coping mechanisms, family support, and economic resources.

General manifestations of asthma. Wheezing, a musical, high-pitched, whistling sound produced by airflow turbulence, is one of the most common symptoms. In the mildest form, wheezing is only end expiratory. As severity increases, the wheeze lasts throughout expiration. In a more severe asthmatic episode, wheezing is also present during inspiration. During a most severe episode,

wheezing may be absent because of the severe limitation of airflow associated with airway narrowing and respiratory muscle fatigue.

Asthma can occur without wheezing when obstruction involves predominantly the small airways. Thus, wheezing is not necessary for the diagnosis of asthma. Furthermore, wheezing can be associated with other causes of airway obstruction, such as cystic fibrosis and heart failure. Patients with vocal cord dysfunction, now referred to as inducible laryngeal obstruction (ILO), have a predominantly inspiratory monophonic wheeze (different from the polyphonic wheeze in asthma), which is heard best over the laryngeal area in the neck. Patients with excessive dynamic airway collapse (EDAC), bronchomalacia, or tracheomalacia also have an expiratory monophonic wheeze heard over the large airways. In exercise-induced bronchoconstriction, wheezing may be present after exercise, and in nocturnal asthma, wheezing is present during the night.

Cough may be the only symptom of asthma, especially in cases of exercise-induced or nocturnal asthma. Usually, the cough is nonproductive and nonparoxysmal. Children with nocturnal asthma tend to cough after midnight and during the early hours of morning. Chest tightness or a history of tightness or pain in the chest may be present with or without other symptoms of asthma, especially in exercise-induced or nocturnal asthma.

Other nonspecific symptoms in infants or young children may be a history of recurrent bronchitis, bronchiolitis, or pneumonia; a persistent cough with colds; and/or recurrent croup or chest rattling. Most children with chronic or recurrent bronchitis have asthma. Asthma is also the most common underlying diagnosis in children with recurrent pneumonia; older children may have a history of chest tightness and/or recurrent chest congestion.

Exercise-induced bronchoconstriction. In patients with exercise-induced bronchoconstriction, the clinical history findings are typical of asthma but are associated only with exercise. Typical symptoms include cough, wheezing, shortness of breath, and chest pain or tightness. Some individuals also may report sore throat or GI upset. Initially, airway dilation is noted during exercise. If

exercise continues beyond approximately 10 minutes, bronchoconstriction supervenes, resulting in asthma symptoms. If the exercise period is shorter, symptoms may develop up to 5-10 minutes after completion of exercise. Higher intensity levels of exercise result in a more intense attack, with running producing more symptoms than walking.

Patients may note asthma symptoms are related to seasonal changes or the ambient temperature and humidity in the environment in which a patient exercises. Other triggers may be pollutants (eg, sulfur, nitrous oxide, ozone) or upper respiratory tract infections. Cold, dry air generally provokes more obstruction than warm, humid air. Consequently, many athletes have good exercise tolerance in sports such as swimming. A prospective longitudinal study in Britain found that swimming was associated with increased lung function and lower risk of asthma-related symptoms, especially among children with respiratory conditions []. [44]

Athletes who are more physically fit may not notice the typical asthma symptoms and may report only a reduced or more limited level of endurance. Several modifiers in the history should prompt an evaluation for causes other than exercise-induced bronchoconstriction. While patients may report typical obstructive symptoms, a history of a choking sensation with exercise, inspiratory wheezing, or stridor should prompt an evaluation for evidence of vocal cord dysfunction.

Physical Examination

The guidelines from the National Asthma Education and Prevention Program highlight the importance of correctly diagnosing asthma, by establishing the following [1]:

- Episodic symptoms of airflow obstruction are present
- Airflow obstruction or symptoms are at least partially reversible
- Exclusion of alternative diagnoses.

Manifestations of an acute episode. Acute episodes can be mild, moderately severe, severe, or characterized by imminent respiratory arrest.

During a **mild episode**, patients may be breathless after physical activity such as walking; they can talk in sentences and lie down; and they may be agitated. Patients with mild acute asthma are able to lie flat. In a mild episode, the respiratory rate is increased, and accessory muscles of respiration are not used. The heart rate is less than 100 bpm, and pulsus paradoxus (an exaggerated fall in systolic blood pressure during inspiration) is not present. Auscultation of the chest reveals moderate wheezing, which is often end expiratory. Rapid forced expiration may elicit wheezing that is otherwise inaudible, and oxyhemoglobin saturation with room air is greater than 95%.

In a **moderately severe episode**, the respiratory rate also is increased. Typically, accessory muscles of respiration are used. In children, also look for supraclavicular and intercostal retractions and nasal flaring, as well as abdominal breathing. The heart rate is 100-120 bpm. Loud expiratory wheezing can be heard, and pulsus paradoxus may be present (10-20 mm Hg). Oxyhemoglobin saturation with room air is 91-95%. Patients experiencing a moderately severe episode are breathless while talking, and infants have feeding difficulties and a softer, shorter cry. In more severe cases, the patient assumes a sitting position.

In a **severe episode**, patients are breathless during rest, are not interested in eating, sit upright, talk in words rather than sentences, and are usually agitated. In a severe episode, the respiratory rate is often greater than 30 per minute. Accessory muscles of respiration are usually used, and suprasternal retractions are commonly present. The heart rate is more than 120 bpm. Loud biphasic (expiratory and inspiratory) wheezing can be heard, and pulsus paradoxus is often present (20-40 mm Hg). Oxyhemoglobin saturation with room air is less than 91%. As the severity increases, the patient increasingly assumes a hunched-over sitting position with the hands supporting the torso, termed the tripod position.

When children are in **imminent respiratory arrest**, in addition to the aforementioned symptoms, they are drowsy and confused, but adolescents may not have these symptoms until they are in frank respiratory failure. In status asthmaticus with imminent respiratory arrest, paradoxical thoracoabdominal

movement occurs. Wheezing may be absent (associated with most severe airway obstruction), and severe hypoxemia may manifest as bradycardia. Pulsus paradoxus noted earlier may be absent; this finding suggests respiratory muscle fatigue.

As the episode becomes more severe, profuse diaphoresis occurs, with the diaphoresis presenting concomitantly with a rise in PCO_2 and hypoventilation. In the most severe form of acute asthma, patients may struggle for air, act confused and agitated, and pull off their oxygen, stating, "I can't breathe." These are signs of life-threatening hypoxia. With advanced hypercarbia, bradypnea, somnolence, and profuse diaphoresis may be present; almost no breath sounds may be heard; and the patient is willing to lie recumbent.

Nonpulmonary Manifestations. Signs of atopy or allergic rhinitis, such as conjunctival congestion and inflammation, ocular shiners, a transverse crease on the nose due to constant rubbing associated with allergic rhinitis, and pale violaceous nasal mucosa due to allergic rhinitis, may be present in the absence of an acute episode, such as during an outpatient visit between acute episodes. Turbinates may be erythematous or boggy. Polyps may be present.

Skin examination may reveal atopic dermatitis, eczema, or other manifestations of allergic skin conditions. Clubbing of the fingers is not a feature of asthma and indicates a need for more extensive evaluation and workup to exclude other conditions, such as cystic fibrosis.

Nocturnal Symptoms. A large percentage of patients with asthma experience nocturnal symptoms once or twice a month. Some patients only experience symptoms at night and have normal pulmonary function in the daytime. This is due, in part, to the exaggerated response to the normal circadian variation in airflow. Children with nocturnal asthma tend to cough after midnight and during the early hours of morning.

Bronchoconstriction is highest between the hours of 4:00 am and 6:00 AM (the highest morbidity and mortality from asthma is observed during this time). These patients may have a more significant decrease in cortisol levels or increased

vagal tone at night. Studies also show an increase in inflammation compared with controls and with patients with daytime asthma.

Staging. Asthma severity is defined as "the intensity of the disease process" prior to initiating therapy and helps in determining the initiation of therapy in a patient who is not on any controller medications [1].

The severity of asthma is classified as the following:

- Intermittent,
- Mild persistent
- Moderate persistent
- Severe persistent

Patients with asthma of any level of severity may have mild, moderate, or severe exacerbations. Some patients with intermittent asthma have severe and life-threatening exacerbations separated by episodes with almost normal lung function and minimal symptoms; however, they are likely to have other evidence of increased bronchial hyperresponsiveness (BHR; exercise or challenge testing) due to ongoing inflammation.

An important point to remember is that the presence of one severe feature is sufficient to diagnose severe persistent asthma. Also, the characteristics in this classification system are general and may overlap because asthma severity varies widely. A patient’s classification may change over time.

Approach Considerations

Laboratory assessments and studies are not routinely indicated for the diagnosis of asthma, but they may be used to exclude other diagnoses. Eosinophilia and elevated serum IgE levels may help guide therapy in some cases. Arterial blood gases and pulse oximetry are valuable for assessing severity of exacerbations and following response to treatment.

Blood and Sputum Eosinophils. Blood eosinophilia greater than 4% or 300-400/μL supports the diagnosis of asthma, but an absence of this finding is not exclusionary. Eosinophil counts greater than 8% may be observed in patients with concomitant atopic dermatitis. This finding should prompt an evaluation for

allergic bronchopulmonary aspergillosis, Churg-Strauss syndrome, or eosinophilic pneumonia.

In assessing asthma control, the British Thoracic Society recommends using sputum eosinophilia determinations to guide therapy [15].

Serum Immunoglobulin E levels greater than 100 IU are frequently observed in patients experiencing allergic reactions, but this finding is not specific for asthma and may be observed in patients with other conditions (eg, allergic bronchopulmonary aspergillosis, Churg-Strauss syndrome). A normal total serum immunoglobulin E level does not exclude the diagnosis of asthma. Elevated serum IgE levels are required for chronic asthma patients to be treated with omalizumab (Xolair).

Arterial Blood Gas (ABG) measurement provides important information in acute asthma. This test may reveal dangerous levels of hypoxemia or hypercarbia secondary to hypoventilation; typically, results are consistent with respiratory alkalosis. Because of the accuracy and utility of pulse oximetry, only patients whose oxygenation is not restored to over 90% with oxygen therapy require an ABG. The clinical picture usually obviates ABGs for most ED patients with acute asthma.

Venous levels of PCO_2 have been tested as a substitute for arterial measurements, and a venous PCO_2 greater than 45 mm may serve as a screening test but cannot substitute for the ABG evaluation of respiratory function.

Hypercarbia is of concern in that it reflects inadequate ventilation and may indicate the need for mechanical ventilation if the PCO_2 is elevated as a result of patient exhaustion; however, the decision to proceed with endotracheal intubation and mechanical ventilation is a clinical assessment.

Periostin is a novel biomarker that is currently under investigation as a diagnostic and treatment adjunct [16]. Evidence suggests that periostin is a marker of Th2/eosinophilic inflammation and airway remodeling that occurs with asthma. While there are no therapies currently approved based on periostin testing, several

investigational medications are being studied with periostin as a predictor of medication effect. Currently, there is no clinical role for routine periostin testing.

Pulse Oximetry Assessment is desirable in all patients with acute asthma to exclude hypoxemia. The hypoxemia of uncomplicated acute asthma is readily reversible by oxygen administration. Oxygenation decreases 4-10 mmHg with beta-agonist inhalant therapy due to increases in V/Q mismatch. Therefore, all patients with acute asthma should have oxygen saturation measured by pulse oximetry, or they simply should be placed on oxygen therapy.

In children, pulse oximetry is often used to grade severity of acute asthma. Oxygen saturation of 97% or above constitutes mild asthma, 92-97% constitutes moderate asthma, and less than 92% signifies severe asthma. Although an isolated pulse oximetry reading at triage is not predictive in most cases (with the notable exception of severe attacks that usually are self-evident on visual inspection), serial monitoring of pulse oximetry status can provide more subtle evidence for or against the need for hospital admission.

Chest Radiography remains the initial imaging evaluation in most individuals with symptoms of asthma. The value of chest radiography is in revealing complications or alternative causes of wheezing and the minor importance of wheezing in the diagnosis of asthma and its exacerbations. Chest radiography usually is more useful in the initial diagnosis of bronchial asthma than in the detection of exacerbations, although it is valuable in excluding complications such as pneumonia and asthma mimics, even during exacerbations.

In most patients with asthma, chest radiography findings are normal or may indicate hyperinflation. Findings may help rule out other pulmonary diseases such as allergic bronchopulmonary aspergillosis or sarcoidosis, which can manifest with symptoms of reactive airway disease. Chest radiography should be considered in all patients being evaluated for asthma to exclude other diagnoses.

Because pneumonia is one of the most common complications of asthma, chest radiography is indicated in patients with fever to rule out pneumonia. With new-onset asthma and eosinophilia, a radiograph may be useful in identifying

prominent streaky infiltrates persisting less than 1 month, indicating Loeffler pneumonia. The infiltrates of Loeffler pneumonia are peripheral with central sparing of the lung fields. These findings have been described as the radiographic negative of pulmonary edema.

Patients with pleuritic chest pain or those with an acute asthmatic episode that responds poorly to therapy, require a chest film to exclude pneumothorax or pneumomediastinum, particularly if subcutaneous emphysema is present.

Chest CT Scanning. High-resolution CT (HRCT) is a second-line examination. It is useful in patients with chronic or recurring symptoms and in those with possible complications such as allergic bronchopulmonary aspergillosis and bronchiectasis [16]. The role of CT in the imaging of airway disease increased after the development of lung HRCT. The technical progress of thin-section acquisition, high-spatial-frequency data reconstruction (ie, bone algorithm technique), and targeted reconstruction has allowed the visualization of finer details on HRCT scans; these details include airtrapping, measurable bronchial wall thickening, atelectasis, centrilobular nodules due to mucous plugging, and acinar nodules due to low-grade inflammatory changes.

HRCT findings in bronchial asthma include the following:

- Bronchial wall thickening
- Bronchial dilatation
- Cylindrical and varicose bronchiectasis
- Reduced airway luminal area
- Mucoid impaction of the bronchi
- Centrilobular opacities, or bronchiolar impaction
- Linear opacities
- Airtrapping, as demonstrated or exacerbated with expiration
- Mosaic lung attenuation, or focal and regional areas of decreased perfusions

Electrocardiography. Patients with asthma who are severely symptomatic should undergo ECG monitoring, as with any seriously ill patient. Sinus

tachycardia and ECG evidence of right heart strain are common in patients with acute asthma. The use of beta$_2$-agonist therapy will cause a paradoxical decrease in heart rate as pulmonary function improves and symptoms are relieved. Supraventricular tachycardia raises the consideration of theophylline toxicity. Arrhythmias, other than supraventricular tachycardia, are rare.

MRI. Aside from cardiovascular applications, MRI of the thorax is used primarily as a problem-solving modality in the workup of patients with lung, mediastinal, or pleural lesions. MRI is a useful alternative to CT pulmonary angiography in evaluating possible pulmonary embolic disease in patients in whom iodinated contrast agent cannot be administered and when the avoidance of ionizing radiation is preferred. In bronchial asthma, the most promising work appears to involve the use of special paramagnetic gases, which amplify the low signal-to-noise ratio of conventional spin-echo and gradient-echo techniques by several thousand times. The use of such gases offsets the disadvantages of the large magnetic susceptibility states with consequent shortened T2 signals induced by the air-alveolar interfaces.

Nuclear medicine technology has been used in the study of aerosol and particulate distribution in the airways. Technetium-99m DTPA radioaerosol lung scintigraphy is a classic technique that shows the extent of major airway distribution, peripheral distribution (depending on particle size), and absorption in the oronasal air passages. Technetium-99m radioaerosol has been used to show improved peripheral lung distribution of corticosteroid both in normal persons and in persons treating their asthma using dry-powder inhalers as opposed to pressurized metered-dose inhalers (pMDIs) with a spacer device. Ventilation scanning with Technetium-99m DTPA has also been used as an indicator of ventilation defects in asthmatic children.

Allergy skin testing is a useful adjunct in individuals with atopy. Results help guide indoor allergen mitigation or help diagnose allergic rhinitis symptoms. The allergens that most commonly cause asthma are aeroallergens such as house dust mites, animal danders, pollens, and mold spores. Two methods are available

to test for allergic sensitivity to specific allergens in the environment: allergy skin tests and blood radioallergosorbent tests (RASTs). Allergy immunotherapy may be beneficial in controlling allergic rhinitis and asthma symptoms for some patients.

Pulmonary Function Testing. Spirometry assessments should be obtained as the primary test to establish the asthma diagnosis. Spirometry should be performed prior to initiating treatment in order to establish the presence and determine the severity of baseline airway obstruction. Optimally, the initial spirometry should also include measurements before and after inhalation of a short-acting bronchodilator in all patients in whom the diagnosis of asthma is considered. Spirometry measures the forced vital capacity (FVC), the maximal amount of air expired from the point of maximal inhalation, and the forced expiratory volume in one second (FEV_1). A reduced ratio of FEV_1 to FVC, when compared with predicted values, demonstrates the presence of airway obstruction. Reversibility is demonstrated by an increase of 12% and 200 mL after the administration of a short-acting bronchodilator.

As a preliminary assessment for exercise-induced asthma (EIA), or exercise-induced bronchospasm (EIB), perform spirometry in all patients with exercise symptoms to determine if any baseline abnormalities (ie, the presence of obstructive or restrictive indices) are present. The assessment and diagnosis of asthma cannot be based on spirometry findings alone because many other diseases are associated with obstructive spirometry indices.

Single-breath counting (SBC) is a novel technique for measuring pulmonary function in children. SBC is the measurement of how far an individual can count using a normal speaking voice after one maximal effort inhalation. The count is in cadence to a metronome that is set at 2 beats per second. A study by Ali et al determined that SBC correlates well with standard measures of pulmonary function. However, further studies are needed to establish values and to evaluate the use in an ED population of **patients with acute asthma exacerbation.**

Bronchoprovocation. Bronchoprovocation testing with either methacholine or histamine is useful when spirometry findings are normal or near normal,

especially in patients with intermittent or exercise-induced asthma symptoms. Bronchoprovocation testing helps determine if airway hyperreactivity is present, and a negative test result usually excludes the diagnosis of asthma. Methacholine is a direct stimulant that acts directly on acetylcholine receptors on smooth muscle, causing contraction and airway narrowing. Methacholine has been reported to have a high sensitivity to identify airway hyperresponsiveness and a negative test is often used to exclude asthma.

Eucapnic hyperventilation with either cold or dry air is an alternative method of bronchoprovocation testing. It has been used to evaluate patients for exercise-induced asthma and has been shown to produce results similar to those of methacholine-challenge asthma testing.

Exercise testing. Exercise spirometry is the standard method for assessing patients with exercise-induced bronchoconstricition. Testing involves 6-10 minutes of strenuous exertion at 85-90% of predicted maximal heart rate and measurement of postexercise spirometry for 15-30 minutes. The defined cutoff for a positive test result is a 15% decrease in FEV_1 after exercise.

Exercise testing may be accomplished in 3 different ways, using cycle ergometry, a standard treadmill test, or free running exercise. This method of testing is limited because laboratory conditions may not subject the patient to the usual conditions that trigger exercise-induced bronchoconstriction symptoms, and results have a lower sensitivity for asthma than other methods.

Allergen-inhalation challenge can be performed in selected patients but are generally not needed or recommended. This test requires an available allergen solution and specialized centers able to handle potentially significant reactions. A negative test finding may allow continued exposure to an allergen (eg, family pet); a positive test finding can dramatically indicate that the patient should avoid a particular allergen. This test is often needed to help diagnose occupational asthma

Mannitol is a provocation test that uses indirect stimuli, causing smooth muscle contraction by release of endogenous mediators, including prostaglandins,

leukotrienes, and histamine. Mannitol is equivalent for the diagnosis of asthma compared with methacholine.

Peak Flow Monitoring. Peak expiratory flow (PEF) measurement is common in the ED because it is inexpensive and portable. Serial measurements document response to therapy and, along with other parameters, are helpful in determining whether to admit the patient to the hospital or discharge from the ED. A limitation of PEF is that it is dependent on effort by the patient. FEV_1 is also effort dependent but less so than PEF. FEV_1 is not often used in the ED except in research settings.

Impulse oscillometry (IOS) is gaining attention for the evaluation of obstructive lung disease, including asthma. IOS uses a speaker to produce pressure oscillations within the airway, resulting in measurement of pressure changes and flows with calculation of resistance, reactance, and resonance. Different frequencies are used to assess large and small airways, which is helpful to determine where the primary obstruction is occurring. For example, a patient with asthma would demonstrate increased resistance at 5 Hz (R5, distal airways) with a normal resistance at 20 Hz (R20, central airways). The primary benefit of IOS is the effort-independent nature of the test, such that small children and frail adults can easily perform the test. Therefore, in patients unable to perform spirometry or with normal spirometry but symptoms suggestive of asthma, IOS could be used to determine if there is increased airway resistance or a bronchodilator response compatible with bronchial hyperreactivity. IOS is also very quickly obtained, but provides no information on lung volumes or oxygen diffusion capacity. Currently, routine use of IOS is limited by a lack of universally accepted reference values across all patient populations.

Exhaled nitric oxide analysis has been shown to predict airway inflammation and asthma control; however, it is technically more complex and not routinely used in the monitoring of patients with asthma.

Sinus CT scanning may be useful to help exclude acute or chronic sinusitis as a contributing factor. In patients with chronic sinus symptoms, CT scanning of

the sinuses can also help rule out chronic sinus disease. Admission chest radiographs showed abnormalities in 50% of the patients and resulted in treatment changes in 5%. The numbers were more remarkable when a paranasal sinus series was obtained in unselected patients who presented primarily because of asthma.

A sinus abnormality of any kind was found in 85% of patients; maxillary sinus abnormalities occurred alone in 63%. In 29% of patients with a sinus abnormality, treatment was immediately altered. All abnormalities were identified on the Waters view alone, which is 6 times more useful than chest radiography in directing the treatment of acute asthma.

24-Hour pH Monitoring can be used to help diagnose gastroesophageal reflux disease (GERD) if a patient's condition is refractory to asthma therapy. Empirical medical therapy is often tried without performing diagnostic tests for GERD, especially if a patient has symptoms of GERD.

Histologic Findings. Asthma is an inflammatory disease characterized by the recruitment of inflammatory cells, vascular congestion, increased vascular permeability, increased tissue volume, and the presence of an exudate. Eosinophilic infiltration, a universal finding, is considered a major marker of the inflammatory activity of the disease.

Histologic evaluations of the airways in a typical patient reveal infiltration with inflammatory cells, narrowing of airway lumina, bronchial and bronchiolar epithelial denudation, and mucus plugs. Additionally, a patient with severe asthma may have a markedly thickened basement membrane and airway remodeling in the form of subepithelial fibrosis and smooth muscle hypertrophy or hyperplasia.

Approach Considerations. Medical care includes treatment of acute asthmatic episodes and control of chronic symptoms, including nocturnal and exercise-induced asthmatic symptoms. Pharmacologic management includes the use of control agents such as inhaled corticosteroids, long-acting bronchodilators (beta-agonists and anticholinergics), theophylline, leukotriene modifiers, and more recent strategies such as the use of anti-immunoglobulin E (IgE) antibodies

(omalizumab) and anti-IL-5 antibodies in selected patients. Relief medications include short-acting bronchodilators, systemic corticosteroids, and ipratropium.

For all but the most severely affected patients, the ultimate goal is to prevent symptoms, minimize morbidity from acute episodes, and prevent functional and psychological morbidity to provide a healthy (or near healthy) lifestyle appropriate to the age of child.

A stepwise (step-up if necessary and step-down when possible) approach to asthma management continues to be used in the current guidelines and is now divided into 3 groups based on age (0-4 y, 5-11 y, 12 y and older) [1].

For all patients, quick-relief medications include rapid-acting $beta_2$-agonists as needed for symptoms. The intensity of treatment depends on the severity of symptoms. If rapid-acting $beta_2$-agonists are used more than 2 days a week for symptom relief (not including use of rapid-acting $beta_2$-agonists for prevention of exercise-induced symptoms), stepping up on treatment may need be considered.

Inhaled corticosteroids are superior to anti-leukotrienes when used as monotherapy in adults and children with persistent asthma. The superiority of inhaled corticosteroids is most pronounced in asthma patients with moderate airway obstruction [17]. The 2015 Global Initiative for Asthma (GINA) guidelines identify inhaled corticosteroids as the preferred controller medication of choice for children and adults.

In general, patients should be assessed every 1-6 months for asthma control. At every visit, adherence, environmental control, and comorbid conditions should be checked. If the patient has good control of their asthma for at least 3 months, treatment can be stepped down; however, the patient should be reassessed in 2-4 weeks to make sure that control is maintained with the new treatment.

Environmental Control. Environmental exposures and irritants can play a strong role in symptom exacerbations. Therefore, in patients who have persistent asthma, the use of skin testing or in vitro testing to assess sensitivity to perennial indoor allergens is important. Once the offending allergens are identified, counsel patients on avoidance from these exposures. In addition, education to avoid

tobacco smoke (both first-hand and second-hand exposure) is important for patients with asthma.

Allergen avoidance takes different forms, depending on the specific allergen size and characteristic. Improvement in symptoms after avoidance of the allergen should result rather rapidly, though the allergen itself (eg, cat dander) may linger in the environment for months after primary removal of the source. A multifaceted approach is necessary, as individual interventions are rarely successful by themselves.

Comprehensive allergen avoidance during the first year of life effectively prevents the onset of asthma in individuals with a high genetic risk, with the effect occurring early in childhood and persisting through adulthood, according to one study. Efforts should focus on the home, where 30-60% of time is spent. Patients should clean and dust their homes regularly [18]. If a patient cannot avoid vacuuming, he or she should use a face mask or a double-bagged vacuum with a high-efficiency particulate air filters. If possible, consideration can be given to moving to a higher floor in the house (less dust and mold) or different neighborhood (fewer cockroaches). Active smoking and exposure to passive smoke must be avoided. Room air ionizers have not been proven to be effective for people with chronic asthma, and the generation of ozone by these machines may be harmful to some. Specific factors related to the home include dust mites, animals, cockroaches, mold, and pollen.

Air pollution caused by traffic may increase the risk of asthma and wheezing, especially in individuals with *EPHX1* gene and enzyme activity. This can be mediated through airway oxidative stress generation.

Dust mites (*Dermatophagoides pteronyssinus* and *farina*, size 30 μm), the primary allergen is an intestinal enzyme on fecal particles. The allergen settles on fabric because of its relatively large size; therefore, air filtration is not very effective. Measures to avoid dust mites include using impervious covers (eg, on mattresses, pillows, comforters, the most important intervention), washing other bedding in hot water (130°F [54.4°C] most effective), removing rugs from the

bedroom, limiting upholstered furniture, reducing the number of window blinds, and putting clothing away in closets and drawers. Minimize the number of soft toys, and wash them weekly or periodically put them in the freezer. Decrease room humidity (< 50%).

The acaricides and extensive bedroom-based environmental control programs may help reduce rhinitis symptoms. If such measures are considered appropriate, they should be the interventions of choice. However, analysis also indicated that isolated use of bedding that is impermeable to house dust mites is not likely to be effective in reducing rhinitis symptoms caused by dust ites.

Animals. Because of the small size (1-20 μm) of dander, saliva, urine, or serum proteins of cats and other animals, these allergens are predominantly airborne indoor allergens. Avoidance involves removing animals from the home (or at least from the bedroom), using dense filtering material over heating and cooling duct vents, and washing cats and dogs as often as twice weekly. The antigens may remain in a home for 6 months or more after cats are removed from the home, and cat antigen may be found in homes and offices where cats were never present, highlighting the importance of frequent cleaning.

Cockroaches. 20% of homes without visible infestation still produce sensitizing levels of cockroach allergen (size 30 μm). Successful allergen elimination measures are difficult, especially in poor living conditions. To control cockroaches, exterminate and use poison baits and traps, keep food out of the bedroom, and never leave food out in the open.

Mold. For indoor molds (size 1-150 μm), avoidance includes keeping areas dry (eg, remove carpets from wet floors), removing old wallpaper, cleaning with bleach products, and storing firewood outdoors.

Pollen (size 1-150 μm) avoidance is difficult or impossible, but efforts to reduce exposure include closing windows and doors, using air conditioning and high-efficiency particulate air filters in the car and home, staying inside during the midday and afternoon when pollen counts are highest, wearing glasses or sunglasses, and wearing a face mask over the nose and mouth when mowing the

lawn. In addition, consider increasing medications preseason and vacationing in a different ecosystem during pollen season.

Management

For all but the most severely affected patients, the ultimate goal is to prevent symptoms, minimize morbidity from acute episodes, and prevent functional and psychological morbidity to provide a healthy (or near healthy) lifestyle appropriate to the age of child.

Pharmacologic management includes the use of relief and control agents. Control agents include inhaled corticosteroids, long-acting bronchodilators (beta-agonists and anticholinergics), theophylline (Theo-24, Theochron, Uniphyl), leukotriene modifiers, anti-IgE antibodies, and IL-5 antibodies. Relief medications include short-acting bronchodilators, systemic corticosteroids, and ipratropium (Atrovent).

The pharmacologic treatment of asthma is based on stepwise therapy. Asthma medications should be added or deleted as the frequency and severity of the patient's symptoms change.

Allergen avoidance. Environmental exposures and irritants can play a strong role in symptom exacerbations. The use of skin testing or in vitro testing to assess sensitivity to perennial indoor allergens is important. Once the offending allergens are identified, counsel patients on how to avoid them. Efforts should focus on the home, where specific triggers include dust mites, animals, cockroaches, mold, and pollen.

Long-Term Monitoring. For all patients with asthma, monitoring should be performed on a continual basis based on the following parameters, which helps in the overall management of the disease:

- Regarding monitoring of asthma signs and symptoms, patients should be taught to recognize inadequate asthma control, and providers should assess control at each visit.
- To monitor pulmonary function, regularly perform spirometry and peak-flow monitoring.

- For quality of life and functional status, inquire about missed work or school days, reduction in activities, sleep disturbances, or change in caregiver activities.
- To monitor the history of asthma exacerbations, determine whether patients are monitoring themselves to detect asthma exacerbations and if these exacerbations are self-treated or treated by health care providers.
- Regarding monitoring pharmacotherapy, ensure compliance with medications and usage of short-acting beta agonists.
- Monitor patient-provider communication and patient satisfaction

Functional Assessment of Airway Obstruction. Perform a functional assessment of airway obstruction with a measurement of the FEV_1 or peak expiratory flow (PEF) initially to assess the patient's response to treatment. PEF measurement is inexpensive and portable. Serial measurements document response to therapy and, along with other parameters, are helpful in the ED setting for determining whether to admit the patient to the hospital or discharge from the ED. A limitation of PEF is that it is dependent on effort by the patient. FEV_1 is also effort dependent but less so than PEF.

Perioperative Considerations. Asthma-related complications associated with surgery include acute bronchoconstriction resulting from intubation, impaired cough, hypoxemia, hypercapnia, atelectasis, respiratory tract infection, and exposure to latex. The likelihood of these complications occurring depends on the severity of the underlying asthma, the type of surgery (thoracic and upper abdominal), and the type of anesthesia.

Patients with asthma should have an evaluation before surgery that includes a review of asthma symptoms, medication use (particularly oral systemic corticosteroids for longer than 2 wk in the past 6 mo), and measurement of pulmonary function. If possible, attempts should be made to improve lung function preoperatively to either predicted values or the personal best level. A short course of oral systemic corticosteroids may be necessary to optimize lung function.

If evidence of airflow obstruction (<80% of baseline values) is present, a brief course of corticosteroids is recommended. Patients who have received oral corticosteroids for an asthma exacerbation in the past 6 mo should receive systemic corticosteroids (100 mg hydrocortisone IV q 8 h) in the perioperative period.

Approach to Level of Activity. Activity is generally limited by patients' ability to exercise and their response to medications. No specific limitations are recommended for patients with asthma, although they should avoid exposure to agents that may exacerbate their disease.

A significant number of patients with asthma also have exercise-induced bronchoconstriction, and baseline control of their disease should be adequate to prevent exertional symptoms. The ability of patients with exercise-induced bronchoconstriction to exercise is based on the level of exertion, degree of fitness, and environment in which they exercise.

Many patients have fewer problems when exercising indoors or in a warm, humid environment than they do outdoors or in a cold, dry environment

Dietary Considerations. Patients with an elevated body mass index have an increased risk for developing asthma. The 2015 GINA guideline adds that obese patients with asthma have lower lung function and more comorbidities than asthma patients who are of normal weight. Asthma is more difficult to control in obese patients, but weight loss of 5-10% can improve asthma control and quality of life [19].

No special diets are generally indicated. Food allergy as a trigger for asthma is uncommon. Unless compelling evidence for a specific allergy exists, milk products do not have to be avoided. Avoidance of foods is recommended after a double-blind food challenge that yields positive results. Sulfites have been implicated in some severe asthma exacerbations and should be avoided in sensitive individuals.

Deterrence. Control of factors contributing to asthma severity is an essential component in asthma treatment. Exposure to irritants or allergens has been shown to increase asthma symptoms and cause exacerbations. Clinicians should evaluate

patients with persistent asthma for allergen exposures and sensitivity to seasonal allergens. Skin testing results should be used to assess sensitivity to perennial indoor allergens, and any positive results should be evaluated in the context of the patient's medical history.

All patients with asthma should be advised to avoid exposure to allergens to which they are sensitive, especially in the setting of occupational asthma. Other factors may include the following:

- Environmental tobacco smoke
- Exertion during high levels of air pollution
- Use of beta blockers
- Avoidance of aspirin and other nonsteroidal anti-inflammatory drugs if the patient is sensitive
- Avoidance of sulfites or other food items/additives to which the patient may be sensitive
- Occupational exposures

Classification Guidelines

The 2007 NAEPP guidelines [1] and the 2009 VA/DoD asthma management guidelines [13] use the severity of asthma classification below, with features of asthma severity divided into three charts to reflect classification in different age groups (0-4 y, 5-11 y, and 12 y and older). Classification includes (1) intermittent asthma, (2) mild persistent asthma, (3) moderate persistent asthma, (4) and severe persistent asthma.

Intermittent asthma is characterized as follows:

- Symptoms of cough, wheezing, chest tightness, or difficulty breathing less than twice a week
- Flare-ups are brief, but intensity may vary
- Nighttime symptoms less than twice a month
- No symptoms between flare-ups
- Lung function test FEV_1 is 80% or more above normal values

- Peak flow has less than 20% variability am-to-am or am-to-pm, day-to-day

Mild persistent asthma is characterized as follows:

- Symptoms of cough, wheezing, chest tightness, or difficulty breathing 3-6 times a week
- Flare-ups may affect activity level
- Nighttime symptoms 3-4 times a month
- Lung function test FEV_1 is 80% or more above normal values
- Peak flow has less than 20-30% variability

Moderate persistent asthma is characterized as follows:

- Symptoms of cough, wheezing, chest tightness, or difficulty breathing daily
- Flare-ups may affect activity level
- Nighttime symptoms 5 or more times a month
- Lung function test FEV_1 is above 60% but below 80% of normal values
- Peak flow has more than 30% variability

Severe persistent asthma is characterized as follows:

- Symptoms of cough, wheezing, chest tightness, or difficulty breathing that are continual
- Frequent nighttime symptoms
- Lung function test FEV_1 is 60% or less of normal values
- Peak flow has more than 30% variability

In contrast, the 2016 Global Initiative for Asthma (GINA) guidelines categorize asthma severity as mild, moderate, or severe. Severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations, as follows [19]:

- Mild asthma: Well controlled with as-needed reliever medication alone or with low-intensity controller treatment such as low-dose inhaled corticosteroids (ICSs), leukotriene receptor antagonists, or chromones

- Moderate asthma: Well controlled with low-dose ICS/long-acting beta2-agonists (LABA)
- Severe asthma: Requires high-dose ICS/LABA to prevent it from becoming uncontrolled, or asthma that remains uncontrolled despite this treatment

The 2013 joint European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines on evaluation and treatment of severe asthma reserves the definition of severe asthma for patients with refractory asthma and those in whom response to treatment of comorbidities is incomplete [20].

The 2016 GINA guidelines stress the importance of distinguishing between severe asthma and uncontrolled asthma, as the latter is a much more common reason for persistent symptoms and exacerbations, and it may be more easily improved. The most common problems that need to be excluded before a diagnosis of severe asthma can be made are the following [19]:

- Poor inhaler technique
- Poor medication adherence
- Incorrect diagnosis of asthma, with symptoms due to alternative conditions such as upper airway dysfunction, cardiac failure, or lack of fitness
- Comorbidities and complicating conditions such as rhinosinusitis, gastroesophageal reflux, obesity, and obstructive sleep apnea
- Ongoing exposure to sensitizing or irritant agents in the home or work environment.

Management Guidelines

The goals for successful management of asthma outlined in the 2007 NHLBI publication "Global Strategy for Asthma Management and Prevention" (see the images below) include the following [1]:

- Achieve and maintain control of asthma symptoms
- Maintain normal activity levels, including exercise
- Maintain pulmonary function as close to normal as possible
- Prevent asthma exacerbations
- Avoid adverse effects from asthma medications

Prevent asthma mortality

Classification of Asthma Severity by Clinical Features Before Treatment
STEP 1: Intermittent
Symptoms less than once a week Brief exacerbations Nocturnal symptoms not more than twice a month • FEV_1 or PEF ≥80% predicted • PEF or FEV_1 variability <20%
STEP 2: Mild Persistent
Symptoms more than once a week but less than once a day Exacerbations may affect activity and sleep Nocturnal symptoms more than twice a month • FEV_1 or PEF ≥80% predicted • PEF or FEV_1 variability 20–30%
STEP 3: Moderate Persistent
Symptoms daily Exacerbations may affect activity and sleep Nocturnal symptoms more than once a week Daily use of inhaled short-acting beta2-agonist • FEV_1 or PEF 60–80% predicted • PEF or FEV_1 variability >30%
STEP 4: Severe Persistent
Symptoms daily Frequent exacerbations Frequent nocturnal asthma symptoms Limitation of physical activities • FEV_1 or PEF ≤60% predicted • PEF or FEV_1 variability >30%

Recommended guidelines for determination of asthma severity based on clinical symptoms, exacerbations, and measurements of airway function. Adapted from Global Strategy for Asthma Management and Prevention: 2002 Workshop Report.

Recommended Medications by Level of Severity: Adults and Children Older than 5 Years		
All Levels: In addition to regular daily controller therapy, rapid-acting inhaled beta2-agonist* should be taken as needed to relieve symptoms, but it should not be taken more than 3 - 4 times per day. Patient education is essential at every level.		
Level of Severity**	**Daily Controller Medications**	**Other Treatment Options*****
Step 1 Intermittent Asthma****	• None necessary	
Step 2 Mild Persistent Asthma	• Low-dose inhaled glucocorticosteroid	• Sustained-release theophylline, or • Cromone, or • Leukotriene modifier
Step 3 Moderate Persistent Asthma	• Low-to-medium inhaled glucocorticosteroid plus long-acting inhaled beta2-agonist	• Medium-dose inhaled glucocorticosteroid plus sustained release theophylline, or • Medium-dose inhaled glucocorticosteroid plus long-acting oral beta2-agonist, or • High-dose inhaled glucocorticosteroid or • Medium-dose inhaled glucocorticosteroid plus leukotriene modifier
Step 4 Severe Persistent Asthma	• High-dose inhaled glucocorticosteroid plus long-acting inhaled beta2-agonist, plus one of more of the following, if needed: • Sustained-release theophylline • Leukotriene modifier • Long-acting oral beta2-agonist • Oral glucocorticosteroid	
All Levels: Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.		

*Other options for reliever medication are (in increasing order of cost) inhaled anticholinergic, short-acting oral beta2-agonist, and short-acting theophylline.
**See Image 2 and Image 4 for classification of severity.
*** Other treatment options listed in order of increasing cost. Relative medication costs may vary from country to country.
****Patients with intermittent asthma but severe exacerbations should be treated as having moderate persistent asthma.

Stepwise pharmacologic therapy

The pharmacologic treatment of asthma is based on stepwise therapy. Asthma medications should be added or deleted as the frequency and severity of the patient's symptoms change. The 2007 NAEPP guidelines offer the recommendations below [1].

Step 1 for intermittent asthma is as follows:

- Controller medication not indicated
- Reliever medication is a short-acting beta-agonist (SABA) as needed for symptoms

Step 2 for mild persistent asthma is as follows:

- Preferred controller medication is a low-dose inhaled corticosteroid
- Alternatives include cromolyn, leukotriene receptor antagonist (LTRA), or theophylline

Step 3 for moderate persistent asthma is as follows:

- Preferred controller medication is either a low-dose inhaled corticosteroid (ICS) plus a long-acting beta-agonist (LABA) (combination medication preferred choice to improve compliance) or an inhaled medium-dose corticosteroid
- Alternatives include an low-dose ICS plus either a LTRA or theophylline

Step 4 for moderate-to-severe persistent asthma is as follows:

- Preferred controller medication is an inhaled medium-dose corticosteroid plus a LABA (combination therapy)
- Alternatives include an inhaled medium-dose corticosteroid plus either an LTRA or theophylline

Step 5 for severe persistent asthma is as follows:

- Preferred controller medication is an inhaled high-dose corticosteroid plus LABA

Step 6 for severe persistent asthma is as follows:

- Preferred controller medication is an inhaled high-dose corticosteroid plus LABA plus oral corticosteroid

The 2016 GINA guidelines include the following stepwise recommendations for medication and symptom control [19]:

- Step 1: As-needed SABA with no controller; other options are to consider low-dose ICS for patients with exacerbation risks
- Step 2: Regular low-dose ICS plus as-needed SABA; other options are LTRA or theophylline
- Step 3: Low-dose ICS/LABA plus as-needed SABA or ICS/formoterol maintenance and reliever therapy; other options are medium-dose ICS or low-dose ICS/LABA
- Step 4: Low-dose ICS/formoterol maintenance and reliever therapy or medium-dose ICS/LABA as maintenance plus as-needed SABA; add-on tiotropium for patients with history of exacerbations; other options are high-dose ICS/LTRA or slow-release theophylline; refer for expert assessment and advice
- Step 5: Refer for expert investigation and add-on treatment; add-on treatments include tiotropium by mist inhaler for patients with a history of exacerbations, omalizumab for severe allergic asthma, and mepolizumab for severe eosinophilic asthma; other options are that some patients may benefit from low-dose oral corticosteroids but long-term systemic adverse effects occur

The 2013 joint European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines include the following additional recommendations for treatment of severe asthma [20]:

- For severe allergic asthma, a therapeutic trial of omalizumab
- Do not use methotrexate or macrolide antibiotics to treat severe asthma
- For severe asthma and recurrent exacerbations of allergic bronchopulmonary aspergillosis (ABPA), antifungal agents should be given

- Do not use antifungal agents for severe asthma without ABPA irrespective of sensitization to fungi (ie, positive skin prick test or fungus-specific immunoglobulin E in serum)

Exercise-Induced Asthma Guidelines

In 2013, the American Thoracic Society released clinical guidelines for the management of exercise-induced bronchoconstriction (EIB), which included the following recommendations [21]:

- Administration of an inhaled SABA before exercise (strong recommendation); the SABA is typically administered 15 minutes before exercise
- A controller agent is added whenever SABA therapy is used daily or more frequently
- Interval or combination warm-up exercise before planned exercise (strong recommendation)
- Recommend against daily use of an inhaled long-acting beta2-agonist as single therapy (strong recommendation)
- For patients who continue to have symptoms despite using an inhaled SABA before exercise or who require an inhaled SABA daily or more frequently: (1) Daily ICS (strong recommendation), (2) Daily administration of an LTRA (strong recommendation), (3) Administration of a mast cell–stabilizing agent before exercise (strong recommendation), and (4) Inhaled anticholinergic agent before exercise (weak recommendation)
- For patients with EIB and allergies who continue to have symptoms despite using an inhaled SABA before exercise or who require an inhaled SABA daily or more frequently consider administration of an antihistamine (weak recommendation)
- For exercise in cold weather, routine use of a device (eg, mask) that warms and humidifies the air during exercise (weak recommendation)

Medication Summary. Quick relief. Long-term control

Asthma medications are generally divided into two categories:

- Quick relief (also called reliever medications)

- Long-term control (also called controller medications)

Quick relief medications are used to relieve acute asthma exacerbations and to prevent exercise-induced bronchoconstriction (EIB) symptoms. These medications include short-acting beta agonists (SABAs), anticholinergics (used only for severe exacerbations), and systemic corticosteroids, which speed recovery from acute exacerbations.

Long-term control medications include inhaled corticosteroids (ICSs), [94, 95], long-acting beta agonists (LABAs),long-acting anticholinergics, combination inhaled corticosteroids and long-acting beta agonists, methylxanthines, and leukotriene receptor antagonists. Inhaled corticosteroids are considered the primary drug of choice for control of chronic asthma, but unfortunately the response to this treatment is characterized by wide variability among patients.

The regular use of ICSs for the treatment of pediatric asthma may suppress linear growth in the first year of treatment, but lower ICS doses may minimize such effects [1,2, 22]. The head-to-head comparison trials are needed to assess the effects of different ICSs, ICS doses, inhalation devices, and patient ages on growth suppression over time.

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TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus consists of an array of dysfunctions characterized by hyperglycemia and resulting from the combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. Poorly controlled type 2 diabetes is associated with an array of microvascular, macrovascular, and neuropathic complications.

Microvascular complications of diabetes include retinal, renal, and possibly neuropathic disease. Macrovascular complications include coronary artery and

peripheral vascular disease. Diabetic neuropathy affects autonomic and peripheral nerves.

Unlike patients with type 1 diabetes mellitus, patients with type 2 are not absolutely dependent on insulin for life. This distinction was the basis for the older terms for types 1 and 2, insulin dependent and non–insulin dependent diabetes.

However, many patients with type 2 diabetes are ultimately treated with insulin. Because they retain the ability to secrete some endogenous insulin, they are considered to require insulin but not to depend on insulin. Nevertheless, given the potential for confusion due to classification based on treatment rather than etiology, the older terms have been abandoned [4]. Another older term for type 2 diabetes mellitus was adult-onset diabetes. Currently, because of the epidemic of obesity and inactivity in children, type 2 diabetes mellitus is occurring at younger and younger ages. Although type 2 diabetes mellitus typically affects individuals older than 40 years, it has been diagnosed in children as young as 2 years of age who have a family history of diabetes. In many communities, type 2 diabetes now outnumbers type 1 among children with newly diagnosed diabetes.

Diabetes mellitus is a chronic disease that requires long-term medical attention to limit the development of its devastating complications and to manage them when they do occur. It is a disproportionately expensive disease; in the US in 2007, the direct medical costs of diabetes were $116 billion, and the total costs were $174 billion; people with diabetes had average medical expenditures 2,3 times those of people without diabetes. The emergency department utilization rate by people with diabetes is twice that of the unaffected population [1, 4].

Etiology of type 2 diabetes mellitus appears to involve complex interactions between environmental and genetic factors. Presumably, the disease develops when a diabetogenic lifestyle (ie, excessive caloric intake, inadequate caloric expenditure, obesity) is superimposed on a susceptible genotype.

The body mass index (BMI) at which excess weight increases risk for diabetes varies with different racial groups. For example, compared with persons of European ancestry, persons of Asian ancestry are at increased risk for diabetes

at lower levels of overweight. Hypertension and prehypertension are associated with a greater risk of developing diabetes in whites than in African Americans [6].

In addition, an in utero environment resulting in low birth weight may predispose some individuals to develop type 2 diabetes mellitus [7]. Infant weight velocity has a small, indirect effect on adult insulin resistance, and this is primarily mediated through its effect on BMI and waist circumference.

About 90% of patients who develop type 2 diabetes mellitus are obese. However, an energy-dense diet may be a risk factor for the development of diabetes that is independent of baseline obesity.

Some studies suggest that environmental pollutants may play a role in the development and progression of type 2 diabetes mellitus [8]. A structured and planned platform is needed to fully explore the diabetes-inducing potential of environmental pollutants.

Secondary diabetes may occur in patients taking glucocorticoids or when patients have conditions that antagonize the actions of insulin (eg, Cushing syndrome, acromegaly, and pheochromocytoma).

Major risk factors for type 2 diabetes mellitus are the following:

- Age greater than 45 years (though, as noted above, type 2 diabetes mellitus is occurring with increasing frequency in young individuals)
- Weight greater than 120% of desirable body weight
- Family history of type 2 diabetes in a first-degree relative (eg, parent or sibling)
- Hispanic, Native American, African American, Asian American, or Pacific Islander descent
- History of previous impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)
- Hypertension (>140/90 mm Hg) or dyslipidemia (HDL cholesterol level < 40 mg/dL or triglyceride level >150 mg/dL)
- History of gestational diabetes mellitus or of delivering a baby with a birth weight of over 9 lb

- Polycystic ovarian syndrome (which results in insulin resistance)

Genetic influences. The genetics of type 2 diabetes are complex and not completely understood. Evidence supports the involvement of multiple genes in pancreatic beta-cell failure and insulin resistance.

Genome-wide association studies have identified dozens of common genetic variants associated with increased risk for type 2 diabetes [5]. Of the variants thus far discovered, the one with the strongest effect on susceptibility is the transcription factor 7-like 2 (*TCF7L2*) gene.

Identified genetic variants account for only about 10% of the heritable component of most type 2 diabetes [5]. An international research consortium found that use of a 40-SNP genetic risk score improves the ability to make an approximate 8-year risk prediction for diabetes beyond that which is achievable when only common clinical diabetes risk factors are used. Moreover, the predictive ability is better in younger persons (in whom early preventive strategies could delay diabetes onset) than in those older than 50 years [9].

Some forms of diabetes have a clear association with genetic defects. The syndrome historically known as maturity onset diabetes of youth (MODY), which is now understood to be a variety of defects in beta-cell function, accounts for 2-5% of individuals with type 2 diabetes who present at a young age and have mild disease. The trait is autosomal dominant and can be screened for through commercial laboratories.

To date, 11 MODY subtypes have been identified, involving mutations in the following genes: HNF-4-alpha, Glucokinase gene, HNF-1-alpha, IPF-1, HNF-1-beta, NEUROD1, KLF11, CEL, PAX4, INS, BLK [10].

Most of the MODY subtypes are associated with diabetes only; however, MODY type 5 is known to be associated with renal cysts, and MODY type 8 is associated with exocrine pancreatic dysfunction [10].

A number of variants in mitochondrial desoxyribonucleic acid (DNA) have been proposed as an etiologic factor for a small percentage of patients with type 2

diabetes. Two specific point mutations and some deletions and duplications in the mitochondrial genome can cause type 2 diabetes and sensorineural hearing loss.

Diabetes can also be a finding in more severe mitochondrial disorders such as Kearns-Sayre syndrome and mitochondrial encephalomyopathy, lactic acidosis, and strokelike episode (MELAS). Mitochondrial forms of diabetes mellitus should be considered when diabetes occurs in conjunction with hearing loss, myopathy, seizure disorder, strokelike episodes, retinitis pigmentosa, external ophthalmoplegia, or cataracts. These findings are of particular significance if there is evidence of maternal inheritance.

Depression. Accumulating evidence suggests that depression is a significant risk factor for developing type 2 diabetes. The relative risk was 1,17 in women with depressed mood and 1,25 in women using antidepressants. Antidepressant use may be a marker of more severe, chronic, or recurrent depression, or antidepressant use itself may increase diabetes risk, possibly by altering glucose homeostasis or promoting weight gain.

Type 2 diabetes has been identified as a risk factor for the development of depression. Depressive symptoms and major depressive disorder are twice as prevalent in patients with type 2 diabetes as in the general population [11].

Schizophrenia has been linked to the risk for type 2 diabetes. Dysfunctional signaling involving protein kinase B (Akt) is a possible mechanism for schizophrenia; moreover, acquired Akt defects are associated with impaired regulation of blood glucose and diabetes, which is overrepresented in first-episode, medication-naive patients with schizophrenia [12]. In addition, second-generation antipsychotics are associated with greater risk for type-2 diabetes.

Preeclampsia and gestational hypertension. A population-based, retrospective cohort study of 1010068 pregnant women examined the association between preeclampsia and gestational hypertension during pregnancy and the risk of developing diabetes post partum. Results showed the incidence rate of diabetes per 1000 person-years was 6,47 for women with preeclampsia and 5,26 for those with gestational hypertension, compared with 2,81 in women with neither

condition. Risk was further elevated in women with preeclampsia or gesntational hypertension comorbid with gestational diabetes.

The prognosis in patients with diabetes mellitus is strongly influenced by the degree of control of their disease. Chronic hyperglycemia is associated with an increased risk of microvascular complications, as shown in the Diabetes Control and Complications Trial (DCCT) in individuals with type 1 diabetes [1] and the UK Prospective Diabetes Study (UKPDS) in people with type 2 diabetes.

Reversion to normal glucose regulation during attempts to prevent progression of pre-diabetes to frank diabetes is a good indicator of slowing disease progression, and it is associated with a better prognosis [13].

Patient Education. No longer is it satisfactory to provide patients who have diabetes with brief instructions and a few pamphlets and expect them to manage their disease adequately. Instead, education of these patients should be an active and concerted effort involving the physician, nutritionist, diabetes educator, and other health professionals. Moreover, diabetes education needs to be a lifetime exercise; believing that it can be accomplished in 1 or 2 encounters is misguided.

For patients with poorly controlled diabetes, individual attention and education is superior to group education [14].

Similarly, a diabetes education and self-management group program in the UK for newly diagnosed patients failed to yield significant benefits. Nonphysician health professionals are usually much more proficient at diabetes education and have much more time for this very important activity.

A systematic review suggested that patients with type 2 diabetes who have a baseline HbA1c of greater than 8% may achieve better glycemic control when given individual education rather than usual care. Outside that subgroup, however, the report found no significant difference between usual care and individual education. In addition, comparison of individual education with group education showed equal impact on HbA1c at 12-18 months.

Patient education is an immensely complex topic, however. The clinical impression of most experts in the field is that there is merit in the provision of careful diabetes education at all stages of the disease.

Prediabetes often precedes overt type 2 diabetes. Prediabetes is defined by a fasting blood glucose level of 100-125 mg/dL or a 2-hour post-oral glucose tolerance test (post-OGTT) glucose level of 140-200 mg/dL. Persons with prediabetes are at increased risk for macrovascular disease, as well as diabetes [1].

Often confused with prediabetes is the metabolic syndrome (also called syndrome X or the insulin-resistance syndrome). Metabolic syndrome, thought to be due to insulin resistance, can occur in patients with overtly normal glucose tolerance, prediabetes, or diabetes. It is diagnosed when a patient has at least 3 of the following 5 conditions:

- Abdominal obesity
- Elevated triglyceride level
- Low level of high-density lipoprotein (HDL) cholesterol
- Elevated blood pressure
- Fasting glucose value of 100 mg/dL or higher.

Eventually, clinically apparent insulin resistance develops. Unfortunately, insulin resistance is not possible to measure clinically, except in research settings. An elevated fasting blood glucose or triglyceride level may be the first indication of insulin resistance. Fasting insulin levels are generally increased at an earlier stage, but they are more directly related to insulin clearance than to insulin resistance. An effort to standardize insulin assays is under way and may allow for the use of fasting insulin levels to diagnose insulin resistance in the future.

Diabetes Testing in Asymptomatic Patients. The U.S. Preventive Services Task Force recommends screening for type 2 diabetes in asymptomatic adults with sustained blood pressure (either treated or untreated) greater than 135/80 mm Hg (grade B recommendation) [3].

The ADA recommends considering testing for prediabetes and diabetes in asymptomatic adults who are overweight (body mass index [BMI] $\geq$25 kg/m^2; may

be lower in at-risk ethnic groups) and have 1 or more of the following additional risk factors [2]:

- Physical inactivity
- First-degree relative with diabetes
- Member of a high-risk ethnic population (eg, African American, Latino, Native American, Asian American, Pacific Islander)
- Delivered a baby weighing over 9 lb or diagnosed with gestational diabetes mellitus
- Hypertension (≥140/90 mm Hg or on therapy for hypertension)
- HDL cholesterol level under 35 mg/dL (0,90 mmol/L) and/or a triglyceride level above 250 mg/dL (2,82 mmol/L)
- Polycystic ovary disease
- IGT or IFG on previous testing
- Other clinical conditions associated with insulin resistance (eg, severe obesity, acanthosis nigricans)
- History of cardiovascular disease

In the absence of the above criteria, the ADA recommends testing for prediabetes and diabetes beginning at age 45 years. If results are normal, testing should be repeated at least every 3 years. More frequent testing may be considered, depending on initial results and risk status.

Approach Considerations. The goals in caring for patients with diabetes mellitus are to eliminate symptoms and to prevent, or at least slow, the development of complications. Microvascular (ie, eye and kidney disease) risk reduction is accomplished through control of glycemia and blood pressure; macrovascular (ie, coronary, cerebrovascular, peripheral vascular) risk reduction, through control of lipids and hypertension, smoking cessation, and aspirin therapy; and metabolic and neurologic risk reduction, through control of glycemia.

New abridged recommendations for primary care providers. The American Diabetes Association has released condensed recommendations for Standards of Medical Care in Diabetes. The abridged version focusses particularly on the following aspects:

- Prediabetes
- Self-management education
- Nutrition
- Physical activity
- Smoking cessation
- Psychosocial care
- Immunizations
- Glycemic treatment
- Therapeutic targets
- Diagnosis and treatment of vascular complications
- Intensification of insulin therapy in type 2 diabetes [15].

Type 2 diabetes care is best provided by a multidisciplinary team of health professionals with expertise in diabetes, working in collaboration with the patient and family [2]. Management includes the following:

- Appropriate goal setting
- Dietary and exercise modifications
- Medications
- Appropriate self-monitoring of blood glucose (SMBG)
- Regular monitoring for complications

- Laboratory assessment.

Ideally, blood glucose should be maintained at near-normal levels (preprandial levels of 90-130 mg/dL and hemoglobin A1C [HbA1c] levels <7%). However, focus on glucose alone does not provide adequate treatment for patients with diabetes mellitus. Treatment involves multiple goals (ie, glycemia, lipids, blood pressure).

Aggressive glucose lowering may not be the best strategy in all patients. Individual risk stratification is highly recommended. In patients with advanced type 2 diabetes who are at high risk for cardiovascular disease, lowering HbA1c to 6% or lower may increase the risk of cardiovascular events.

A study from the ACCORD Study Group found that setting the treatment target for HbA1c below 6% in high-risk patients resulted in reduced 5-year nonfatal myocardial infarctions. However, patients who did not achieve the treatment target experienced increased 5-year mortality.

Review of blood glucose logs must be part of any diabetes management plan. Both iron and erythropoietin treatments commonly prescribed in patients with chronic kidney disease cause a significant increase in HbA1c without affecting blood glucose levels.

With each health-care system encounter, patients with diabetes should be educated about and encouraged to follow an appropriate treatment plan. Adherence to diet and exercise should continue to be stressed throughout treatment, because these lifestyle measures can have a large effect on the degree of diabetic control that patients can achieve.

More frequent visits with a primary care provider (every 2 wk) led to markedly rapid reductions in serum glucose, HbA1c, and low-density lipoprotein (LDL) cholesterol levels. However, how such a strategy can work globally remains a challenge due to available resources and economic restrictions [16].

Pharmacologic Therapy. Early initiation of pharmacologic therapy is associated with improved glycemic control and reduced long-term complications in

type 2 diabetes. Drug classes used for the treatment of type 2 diabetes include the following:

- Biguanides
- Sulfonylureas
- Meglitinide derivatives
- Alpha-glucosidase inhibitors
- Thiazolidinediones (TZDs)
- Glucagonlike peptide-1 (GLP-1) agonists
- Dipeptidyl peptidase IV (DPP-4) inhibitors
- Selective sodium-glucose transporter-2 (SGLT-2) inhibitors
- Insulins
- Amylinomimetics
- Bile acid sequestrants
- Dopamine agonists

Management of Glycemia. In 2013, the American Association of Clinical Endocrinologists (AACE) issued a comprehensive new type 2 diabetes treatment algorithm - the first to incorporate obesity, prediabetes, and cardiovascular risk factor management [17].

Obesity management was incorporated into the algorithm because it is now clear that weight loss also reduces blood glucose. The authors suggest that obesity management can be considered first-line treatment for people with prediabetes. The prediabetes section of the algorithm considers cardiovascular risk factors and the options of antihyperglycemic or antiobesity therapy, though without making a recommendation regarding which form of treatment is better.

As in the AACE's earlier glycemic-control algorithm, the level of treatment depends on the initial hemoglobin A1c. (Lifestyle modification, including weight loss, is a component of all treatments.) Whereas the earlier algorithm recommended an HbA1c of 6,5% or lower as the goal for most patients, the current algorithm refines this advice, recommending an HbA1c of 6,5% or lower for healthy patients without concurrent illness and at low risk for hypoglycemia but

individualized target HbA1c values greater than 6,5% for patients with concurrent illness and those who are at risk for hypoglycemia.

Table 16

Treatment of Type 2 Diabetes Mellitus

Category of patients	monotherapy*	add	add
obese	metformin	sulfonylurea	exenatide or insulin or glitazone
non-obese	Sulfonylurea or metformin	metformin or sulfonylurea	exenatide or insulin or glitazone
elderly	low dose secretagogue	Switch to simple insulin regimen	-------
Asians	glitazone	metformin	sulfonylurea or insulin or exenatide**

*for symptomatic patients, may iritialy use secretagogue or insulin to rapidy decrease glucose

** exenatide not approved for use with glitazone

Dietary Modifications. For most patients, the best diet is one consisting of the foods that they are currently eating. Attempts to calibrate a precise macronutrient composition of the diet to control diabetes, while time-honored, are generally not supported by the research. Caloric restriction is of first importance. After that, individual preference is reasonable.

Modest restriction of saturated fats and simple sugars is also reasonable. However, some patients have remarkable short-term success with high-fat, low-carbohydrate diets of various sorts. Therefore, the author always stresses weight management in general and is flexible regarding the precise diet that the patient consumes. Also, the practitioner should advocate a diet composed of foods that are within the financial reach and cultural milieu of the patient. For example, patients who participate in Ramadan may be at higher risk of acute diabetic complications. Although these patients do not eat during the annual observance, they should be encouraged to actively monitor their glucose, alter the dosage and timing of their

medication, and seek dietary counseling and patient education to counteract any complications [18].

Weight loss. Modest weight losses of 5-10% have been associated with significant improvements in cardiovascular disease risk factors (ie, decreased HbA1c levels, reduced blood pressure, increase in HDL cholesterol, decreased plasma triglycerides) in patients with type 2 diabetes mellitus. Risk factor reduction was even greater with losses of 10-15% of body weight [19].

A study by Lazo et al attested to the benefits of lifestyle intervention, which aimed at a minimum weight loss of 7%, on hepatic steatosis in patients with type 2 diabetes. Since there is no known treatment for nonalcoholic fatty liver disease, a weight loss strategy may help to prevent progression to serious liver damage.

Mediterranean-style diet. Esposito et al reported greater benefit from a low-carbohydrate, Mediterranean-style diet than from a low-fat diet in patients with newly diagnosed type 2 diabetes mellitus [20].

In a single-center, randomized trial, overweight patients with newly diagnosed type 2 diabetes mellitus who had never been treated with antihyperglycemic drugs and whose HbA1c levels were less than 11% were assigned to either a Mediterranean-style diet (<50% of daily calories from carbohydrates) or a low-fat diet (<30% of daily calories from fat). After 4 years, participants assigned to the Mediterranean-style diet had lost more weight and had demonstrated more improvement in some measures of glycemic control and coronary risk than had participants consuming the low-fat diet; 44% of patients in the Mediterranean-style diet group required antihyperglycemic drug therapy, compared with 70% of those in the low-fat diet group.

High-protein versus high-carbohydrate diet. The long-term therapeutic effect of a high-protein diet is not superior to that of a high-carbohydrate diet in the treatment of type 2 diabetes mellitus. In this 12-month trial, 99 overweight or obese diabetic patients followed a low-fat diet (30% total energy) that was either high in protein (30% total energy) or high in carbohydrate (55% total energy); both groups benefited equally.

It should also be noted that already-attenuated glucose disposal is not worsened by postprandial circulating amino acid concentration. Therefore, recommendations to restrict dietary proteins in patients with type 2 diabetes seem unwarranted.

Trans-palmitoleate. In the Cardiovascular Health Study, phospholipid *trans*-palmitoleate levels were found to be associated with lower metabolic risk. *Trans*-palmitoleate is principally derived from naturally occurring dairy and other ruminant *trans*-fats. Circulating *trans*-palmitoleate is associated with lower insulin resistance, incidence of diabetes, and atherogenic dyslipidemia. Potential health benefits, therefore, need to be explored.

Advanced glycation end products. Food-derived, pro-oxidant, advanced glycation end products may contribute to insulin resistance in clinical type 2 diabetes mellitus and may suppress protective mechanisms. Advanced glycation end-product restriction may preserve native defenses and insulin sensitivity by maintaining a lower basal oxidative state.

Other considerations. Oral ginseng (or ginsenoside) does not improve pancreatic beta-cell function. Routine use is not recommended.

Pasta enriched with biologically active isoflavone aglycons improves endothelial function in patients with type 2 diabetes mellitus and favorably affects cardiovascular disease risk markers.

In patents with type 2 diabetes mellitus, impaired fasting glucose or impaired glucose tolerance at high risk for cardiovascular disease, addition of omega-3 fatty acids does not reduce risk of cardiovascular events, including death from cardiovascular causes [21].

Activity Modifications. Most patients with type 2 diabetes mellitus can benefit from increased activity. Aerobic exercise improves insulin sensitivity and may improve glycemia markedly in some patients.

Structured exercise training of more than 150 minutes per week is associated with greater HbA1c reduction; however, physical activity helps lower HbA1c only when combined with dietary modifications.

The patient should choose an activity that she or he is likely to continue. Walking is accessible to most patients in terms of time and financial expenditure.

A previously sedentary patient should start activities slowly. Older patients, patients with long-standing disease, patients with multiple risk factors, and patients with previous evidence of atherosclerotic disease should have a cardiovascular evaluation, probably including an imaging study, prior to beginning a significant exercise regimen.

A supervised, facility-based exercise training program, when added to standard treatments for type 2 diabetes mellitus, yields better results than does simply counseling patients to exercise.

A randomized, controlled trial by Church et al emphasized the need to incorporate both aerobic and resistance training to achieve better lowering of HbA1c levels. Aerobic exercise alone or in combination with resistance training improves glycemic control, circulating triglycerides, systolic blood pressure, and waist circumference [22]. The impact of resistance exercise alone, however, remains unclear.

Long-term endurance and strength training resulted in improved metabolic control of diabetes mellitus and significant cardiovascular risk reduction, compared with standard treatment. However, exercise training did not improve conduit arterial elasticity.

Yoga can be effective in reducing oxidative metabolic stress in patients with type 2 diabetes mellitus. However, yoga did not impact waist-to-hip ratio, blood pressure, vitamin E, or superoxide dismutase.

Monitoring for Diabetic Complications. The ADA recommends initiation of complications monitoring at the time of diagnosis of diabetes mellitus [2]. This regimen should include yearly dilated eye examinations, annual microalbumin checks, and foot examinations at each visit.

Middle-aged and older adults with diabetes have an increased risk for the development of geriatric conditions (eg, cognitive, vision, and hearing impairments; falls). These conditions substantially contribute to morbidity and

functional impairment. The authors concluded that adults with diabetes should be monitored for the development of geriatric conditions at a younger age than was previously considered.

The risk for early development of Parkinson disease is 36% higher in patients with diabetes mellitus. However, a systematic review from Cereda et al found no conclusive evidence of this association.

A high overall risk for pancreatic neoplasm is noted in individuals with diabetes mellitus, particularly in those aged 45-65 years.

The incidence of complications widely varies among the Asian subgroups, suggesting the need for an ethnic stratified nuanced approach in evaluation and surveillance [23]. One size does not fit all.

Prevention of Type 2 Diabetes Mellitus. Guidelines from the American College of Clinical Endocrinologists for the prevention of type 2 diabetes mellitus in patients at risk recommend the following measures:

- Weight reduction
- Proper nutrition
- Regular physical activity
- Cardiovascular risk factor reduction
- Aggressive treatment of hypertension and dyslipidemia

Lifestyle improvement. The modest lifestyle changes (eg, 4-5% sustained weight reduction for approximately 3 y) reduce the risk for diabetes in patients at high risk by 58% [24]. Eight health-care facilities participated in an instructive study of group-based lifestyle intervention that should help other agencies/states emulate strategies used to affect positive lifestyle changes for the prevention of diabetes.

In an 11-year, population-based cohort study of over 200000 men and women without evidence of diabetes, heart disease, or cancer at baseline, good lifestyle decisions in combination significantly reduced the risk of developing diabetes. For each additional positive lifestyle factor (eg, with regard to diet,

physical activity, or smoking) in the low-risk group, the odds for diabetes were 31% lower [25].

The cigarette smokers are at increased risk for type 2 diabetes, smoking cessation leads to higher short-term risk.

The adjusted hazard ratio of incident diabetes among persons in the highest tertile of pack-years was 1,42, compared with persons who had never smoked. However, in the first 3 years after quitting smoking, the hazard ratio was 1,73; the risk then gradually decreased, disappearing completely at 12 years. Yeh et al recommended that smoking cessation in smokers at risk for diabetes be coupled with strategies for prevention and early detection of diabetes.

A significant inverse correlation has been found between the risk of diabetes and the intake of magnesium, which plays an important role in insulin action and glucose homeostasis. In a meta-analysis, the summary relative risk of type 2 diabetes for every 100 mg/day increment in magnesium intake was 0,86.

Interest in the impact of phylloquinone intake on glucose tolerance and insulin sensitivity has a long history. A 2012 report suggests a beneficial role for phylloquinone in diabetes prevention in elderly subjects with high cardiovascular risk. However, caution is advised in patients who are concurrently being treated with anticoagulant drugs such as warfarin [26].

Pharmacologic prevention. Drugs from several classes have been studied in the prevention of diabetes. However, the FDA has not approved any drug for the treatment of prediabetes or the prevention of type 2 diabetes.

Metformin. The ADA recommends that, in addition to lifestyle counseling, metformin be considered in selected patients with prediabetes [2]. ADA criteria for preventive metformin therapy are as follows:

- Obesity
- Age younger than 60 years
- Both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)

- Other risk factors (eg, HbA1C >6%, hypertension, low HDL cholesterol, elevated triglycerides, or a family history of diabetes in a first-degree relative).

In the DPP, metformin 1700 mg daily was about half as effective as lifestyle intervention in reducing risk among subjects with elevated fasting and postload plasma glucose concentrations [24]. Over an average follow-up period of 2,8 years, the incidence of diabetes was 11,0, 7,8, and 4,8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively.

Thiazolidinediones. Troglitazone was effective in preventing diabetes. This effect was also seen in the Troglitazone in Prevention of Diabetes (TRIPOD) study of Hispanic women with a history of gestational diabetes. After troglitazone was withdrawn from the market because of hepatotoxicity, the continuation of TRIPOD in the Pioglitazone in the Prevention of Diabetes Study demonstrated slowed progression of subclinical atherosclerosis with glitazone treatment.

In the Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) trial, investigators concluded that rosiglitazone at 8 mg daily reduces the incidence of type 2 diabetes mellitus in patients with IFG and/or IGT. At the end of this prospective, multicenter study, composite outcome of diabetes or death from any cause was 11,6% in the rosiglitazone group versus 26% in the placebo group. Ramipril did not produce significant reduction in the same composite outcome [27].

Acarbose (100 mg three times a day) was shown in the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) to reduce diabetes rates by approximately 25% in patients at high risk for the development of type 2 diabetes [27]. This 6-year, international, multicenter, double-blind, placebo-controlled, randomized investigation included 1368 subjects with IGT.

Stroke Prevention in Diabetes. The 2010 American Heart Association/American Stroke Association (AHA/ASA) guidelines for the primary prevention of stroke include the following recommendations for patients with diabetes:

- Regular blood pressure screening
- Physical activity; 30 minutes or more of moderate-intensity activity on a daily basis
- A low-sodium, high-potassium diet to reduce blood pressure; a diet emphasizing consumption of fruits, vegetables, and low-fat dairy products (eg, the Dietary Approaches to Stop Hypertension [DASH] diet) may lower stroke risk
- A blood pressure goal of less than 130/80 mm Hg
- Drug therapy with ACE inhibitors or ARBs
- Statin therapy, especially in patients with other risk factors; monotherapy with fibrates may also be considered to lower stroke risk.

The AHA/ASA guidelines note that the benefit of taking aspirin for the reduction of stroke risk has not been fully demonstrated in diabetic patients.

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OBESITY

Obesity is one of the greatest public health challenges of the 21st century. Its prevalence has tripled in many countries of the WHO European Region since the 1980s, and the numbers of those affected continue to rise at an alarming rate, particularly among children. In addition to causing various physical disabilities and psychological problems, excess weight drastically increases a person's risk of developing a number of noncommunicable diseases (NCDs), including cardiovascular disease, cancer and diabetes. The risk of developing more than one of these diseases (co-morbidity) also increases with increasing body weight. Obesity is already responsible for 2–8% of health costs and 10–13% of deaths in different parts of the Region.

Both societies and governments need to act to curb the epidemic. National policies should encourage and provide opportunities for greater physical activity, and improve the affordability, availability and accessibility of healthy foods. They should also encourage the involvement of different government sectors, civil society, the private sector and other stakeholders.

The annual cost of managing obesity in the US alone amounts to approximately $190.2 billion per year, or 20.6% of national health expenditures, according to a recent study [3].

In a 2016 position statement, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) proposed a new name for obesity, adiposity-based chronic disease (ABCD). The AACE/ACE did not introduce the name as an actual replacement for the term obesity but instead as a means of helping the medical community focus on the pathophysiologic impact of excess weight [4].

Measurements of obesity

Obesity represents a state of excess storage of body fat. Although similar, the term overweight is puristically defined as an excess of body weight for height. Normal, healthy men have a body fat percentage of 15-20%, while normal, healthy

women have a percentage of approximately 25-30% [5]. However, because differences in weight among individuals are only partly the result of variations in body fat, body weight is a limited, although easily obtained, index of obesity.

The body mass index (BMI), also known as the Quetelet index, is used far more commonly than body fat percentage to define obesity. In general, BMI correlates closely with the degree of body fat in most settings; however, this correlation is weaker at low BMIs.

An individual's BMI is calculated as weight/height^2, with weight being in kilograms and height being in meters (otherwise, the equation is weight in pounds 0.703/height in inches^2). Online BMI calculators are available.

A person's body fat percentage can be indirectly estimated by using the Deurenberg equation, as follows:

body fat percentage = 1.2(BMI) + 0.23(age) - 10.8(sex) - 5.4

with age being in years and sex being designated as 1 for males and 0 for females. This equation has a standard error of 4% and accounts for approximately 80% of the variation in body fat.

Although the BMI typically correlates closely with percentage body fat in a curvilinear fashion, some important caveats apply to its interpretation. In mesomorphic (muscular) persons, BMIs that usually indicate overweight or mild obesity may be spurious, whereas in some persons with sarcopenia (eg, elderly individuals and persons of Asian descent, particularly from South Asia), a typically normal BMI may conceal underlying excess adiposity characterized by an increased percentage of fat mass and reduced muscle mass.

In view of these limitations, some authorities advocate a definition of obesity based on percentage of body fat. For men, a percentage of body fat greater than 25% defines obesity, with 21-25% being borderline. For women, over 33% defines obesity, with 31-33% being borderline.

Other indices used to estimate the degree and distribution of obesity include the 4 standard skin thicknesses (ie, subscapular, triceps, biceps, suprailiac) and various anthropometric measures, of which waist and hip circumferences are the

most important. Skinfold measurements are the least accurate means by which to assess obesity.

Dual-energy radiographic absorptiometry (DXA) scanning is used primarily by researchers to accurately measure body composition, particularly fat mass and fat-free mass. It has the additional advantage of measuring regional fat distribution. However, DXA scans cannot be used to distinguish between subcutaneous and visceral abdominal fat deposits.

The current standard techniques for measuring visceral fat volume are abdominal computed tomography (CT) scanning (at L4-L5) and magnetic resonance imaging (MRI) techniques. A simpler technique, using bioelectrical impedance, was recently introduced [5]. However, these methods are limited to clinical research.

Classification of obesity

Although several classifications and definitions for degrees of obesity are accepted, the most widely accepted classifications are those from the World Health Organization (WHO), based on BMI. The WHO designations include the following:

- Grade 1 overweight (commonly and simply called overweight) - BMI of 25-29.9 kg/m^2
- Grade 2 overweight (commonly called obesity) - BMI of 30-39.9 kg/m^2
- Grade 3 overweight (commonly called severe or morbid obesity) - BMI greater than or equal to 40 kg/m^2

The cut-off for each grade varies according to an individual's ethnic background. For example, a BMI of 23 kg/m^2 or higher may define grade 1 overweight and 27.5 kg/m^2 or higher may define grade 2 overweight (obesity) in many Asian populations, in which the risk was shown to be high and extremely high for grade 1 and 2 overweight at these levels, respectively. Other BMI cutoffs identified as potential public health action points in these populations are 32.5 and 37.5 kg/m^2.

The surgical literature often uses a different classification to recognize particularly severe obesity. The categories are as follows:

- Severe obesity - BMI greater than 40 kg/m ^{2}
- Morbid obesity - BMI of 40-50 kg/m ^{2}
- Super obese - BMI greater than 50 kg/m ^{2}

In children, a BMI above the 85th percentile (for age-matched and sex-matched control subjects) is commonly used to define overweight, and a BMI above the 95th percentile is commonly used to define obesity.

Comorbidities associated with obesity. Obesity is associated with a host of potential comorbidities that significantly increase the risk of morbidity and mortality in obese individuals. Although no cause-and-effect relationship has been clearly demonstrated for all of these comorbidities, amelioration of these conditions after substantial weight loss suggests that obesity probably plays an important role in their development.

Apart from total body fat mass, the following aspects of obesity have been associated with comorbidity:

- Fat distribution
- Waist circumference
- Age of obesity onset
- Intra-abdominal pressure

Fat distribution. Accumulating data suggest that regional fat distribution substantially affects the incidence of comorbidities associated with obesity [1]. Android obesity, in which adiposity is predominantly abdominal (including visceral and, to a lesser extent, subcutaneous), is strongly correlated with worsened metabolic and clinical consequences of obesity.

Waist circumference. The thresholds used in the National Cholesterol Education Program Adult Treatment Panel III definition of metabolic syndrome state that significantly increased cardiovascular risk (metabolic central obesity) exists in men with waist circumferences of greater than 94 cm (37 in) and in women with waist circumferences of greater than 80 cm (31.5 in), as well as waist-

to-hip ratios of greater than 0.95 in men and of greater than 0.8 in women. Circumferences of 102 cm (40 in) in men and 88 cm (35 in) in women indicate a markedly increased risk requiring urgent therapeutic intervention.

These thresholds are much lower in Asian populations: a waist circumference of greater than 90 cm in men and of more than 80 cm in women were more appropriate criteria for metabolic central obesity in these ethnic groups [6].

Age of obesity onset. An elevated BMI during adolescence (starting within the range currently considered normal) is strongly associated with the risk of developing obesity-related disorders later in life, independent of adult BMI. Increases in BMI during early adulthood (age 25-40 y) are associated with a worse profile of biomarkers related to obesity than are BMI increases during later adulthood. This is consistent with most emerging data regarding timing of changes in BMI and later health consequences.

Intra-abdominal pressure. Apart from the metabolic complications associated with obesity, a paradigm of increased intra-abdominal pressure has been recognized. This pressure effect is most apparent in the setting of marked obesity (BMI $\geq$ 50 kg/m^2) and is espoused by bariatric surgeons [8]. Findings from bariatric surgery and animal models suggest that this pressure elevation may play a role (potentially a major one) in the pathogenesis of comorbidities of obesity, such as the following:

- Pseudotumor cerebri
- Lower-limb circulatory stasis
- Ulcers
- Dermatitis
- Thrombophlebitis
- Reflux esophagitis
- Abdominal hernias
- Possibly, hypertension and nephrotic syndrome

Additional comorbidities. Overweight and obese individuals are at increased risk for the following health conditions:

- Metabolic syndrome
- Type 2 diabetes
- Hypertension
- Dyslipidemia
- Coronary heart disease
- Osteoarthritis
- Stroke
- Depression
- Non-alcoholic fatty liver disease (NAFLD)
- Infertility (women) and erectile dysfunction (men)
- Risk of stillbirth
- Gall bladder disease
- Obstructive sleep apnea
- Gastroesophageal reflux disease (GERD)
- Some cancers (eg, endometrial, breast, and colon) [2]
- Asthma

Osteoarthritis. A study by Losina et al found that obesity with knee osteoarthritis resulted in the loss of a substantial number of quality-adjusted life years. The association was most notable among black and Hispanic women [9].

Focal glomerulosclerosis. Some reports suggest an association between severe obesity and focal glomerulosclerosis [10]. This complication, in particular, improves substantially or resolves soon after bariatric surgery, well before clinically significant weight loss is achieved.

Pickwickian syndrome. The so-called Pickwickian syndrome is a combined syndrome of obesity-related hypoventilation and sleep apnea. It is named after Charles Dickens's novel "The Pickwick Papers", which contains an obese character who falls asleep constantly during the day.

The hypoventilation in Pickwickian syndrome results from severe mechanical respiratory limitations to chest excursion, caused by severe obesity. The sleep apnea may be from obstructive and/or central mechanisms. Obstructive sleep apnea is common among men with collar size greater than 17 in (43 cm) and women with collar size greater than 16 in (41 cm).

Increased and decreased sleep duration. Sleep duration of less than 5 hours or more than 8 hours was associated with increased visceral and subcutaneous body fat, in a study of young African Americans and Hispanic Americans. This association relates mostly to decreased leptin hormone and increased ghrelin hormone levels [11].

Pathophysiology

Hypertrophic versus hypercellular obesity

The adipocyte, which is the cellular basis for obesity, may be increased in size or number in obese persons. Hypertrophic obesity, characterized by enlarged fat cells, is typical of android abdominal obesity. Hypercellular obesity is more variable than hypertrophic obesity; it typically occurs in persons who develop obesity in childhood or adolescence, but it is also invariably found in subjects with severe obesity.

Hypertrophic obesity usually starts in adulthood, is associated with increased cardiovascular risk, and responds quickly to weight reduction measures. In contrast, patients with hypercellular obesity may find it difficult to lose weight through nonsurgical interventions.

Adipocytes

Products. The adipocyte is increasingly found to be a complex and metabolically active cell. At present, the adipocyte is perceived as an active endocrine gland producing several peptides and metabolites that may be relevant to the control of body weight; these are being studied intensively.

Many of the adipocytokines secreted by adipocytes are proinflammatory or play a role in blood coagulation. Others are involved in insulin sensitivity and

appetite regulation. However, the function of many of these identified cytokines remains unknown or unclear.

Proinflammatory products of the adipocyte include the following [12]

- Tumor necrosis factor-alpha
- Interleukin 6
- Monocyte chemoattractant protein-1 (MCP-1)

Other adipocyte products include the following [12]

- Lipotransin
- Plasminogen activator inhibitor-1 (PAI-1) - Associated with cardiovascular risk
- Adipocyte lipid-binding protein
- Acyl-stimulation protein
- Prostaglandins - Coagulation role
- Adipsin
- Perilipins
- Lactate
- Leptin - Appetite regulator
- Adiponectin - Major role in insulin sensitivity
- Monobutyrin
- Phospholipid transfer protein

Metabolism and function. Critical enzymes involved in adipocyte metabolism and function include the following:

- Endothelial-derived lipoprotein lipase - Lipid storage
- Hormone-sensitive lipase - Lipid elaboration and release from adipocyte depots
- Acyl-coenzyme A (acyl-CoA) synthetases - Fatty acid synthesis

In addition, a cascade of enzymes is involved in beta-oxidation and fatty acid metabolism. The ongoing flurry of investigation into the intricacies of adipocyte metabolism has not only improved our understanding of the pathogenesis of obesity but has also offered several potential targets for therapy.

Development. The recognition that the differentiation of preadipocytes to adipocytes ss occurs in white and brown adipose tissue, even in adults, has increased its potential importance in the development of obesity and the relapse to obesity after weight loss.

Among the identified elements in this process are the following transcription factors:

- Peroxisome proliferator-activated receptor–gamma (PPAR-gamma)
- Retinoid-X receptor ligands
- Perilipin
- Adipocyte differentiation–related protein (ADRP)
- CCAAT/enhancer-binding proteins (C/EBP) alpha, beta, and delta

PPAR-gamma agonists increase the recruitment, proliferation, and differentiation of preadipocytes (healthy fat) and cause apoptosis of hypertrophic and dysfunctional adipocytes (including visceral fat). This results in improved fat function and improved metabolic parameters associated with excessive fat–related metabolic diseases (EFRMD), including type 2 diabetes mellitus, hypertension, and dyslipidemia [13].

Hormonal influences on appetite. Many hormones affect appetite and food intake. Endocannabinoids, through their effects on endocannabinoid receptors, increase appetite, enhance nutrient absorption, and stimulate lipogenesis. Melanocortin hormone, through its effects on various melanocortin receptors, modifies appetite.

Several gut hormones play significant roles in inducing satiety, including glucagonlike peptide-1 (GLP-1), neuropeptide YY (PYY), and cholecystokinin. Leptin and pancreatic amylin are other potent satiety hormones. On the other hand, ghrelin, which is secreted from the stomach fundus, is a major hunger hormone.

Odor detection threshold. Smell plays an important role in feeding behavior. Increased insulin led to reduced smelling capacity, potentially reducing the pleasantness of eating. Therefore, insulin action in the olfactory bulb may be

involved in the process of satiety and may be of clinical interest as a possible factor in the pathogenesis of obesity.

Leptin (from the Greek word *leptos*, meaning thin) was discovered in 1994 and ushered in an explosion of research and a great increase in knowledge about regulation of the human feeding and satiation cycle. Leptin is a 16-kd protein produced predominantly in white subcutaneous adipose tissue and, to a lesser extent, in the placenta, skeletal muscle, and stomach fundus in rats. Leptin has myriad functions in carbohydrate, bone, and reproductive metabolism that are still being unraveled, but its role in body-weight regulation is the main reason it came to prominence.

Potentially, leptin sensitizers may assist in changing feeding habits.

The major role of leptin in body-weight regulation is to signal satiety to the hypothalamus and thus reduce dietary intake and fat storage while modulating energy expenditure and carbohydrate metabolism, preventing further weight gain. Unlike the Ob/Ob mouse model in which this peptide was first characterized, most humans who are obese are not leptin deficient but are instead leptin resistant. Therefore, they have elevated levels of circulating leptin. Leptin levels are higher in women than in men and are strongly correlated with BMI [14].

Patients with night-eating syndrome have attenuation of the nocturnal rise in plasma melatonin and leptin levels and higher circadian levels of plasma cortisol. These individuals have morning anorexia, evening hyperphagia, and insomnia[14].

Genetics. Mutations resulting in defects of the leptin receptor in the hypothalamus may occur. These mutations result in early onset obesity and hyperphagia despite normal or elevated leptin levels, along with hypogonadotropic hypogonadism, and defective thyrotropin secretion.

Etiology

The etiology of obesity is far more complex than simply an imbalance between energy intake and energy output. Although this view allows easy conceptualization of the various mechanisms involved in the development of obesity, obesity is far more than simply the result of eating too much and/or

exercising too little. Possible factors in the development of obesity include the following:

- Metabolic factors
- Genetic factors are presumed to explain 40-70% of the variance in obesity, within a limited range of BMI (18-30 kg/m^2). Metabolic rate, spontaneous physical activity, and thermic response to food seem to be heritable to a variable extent.
- Level of activity: the prevalence of inactivity in industrialized countries is considerable and relevant to the rise in obesity. Hypercortisolism associated with recurrent affective disorders increases the risk for metabolic disorders and cardiovascular risk factors such as obesity, overweight, large waist, high low-density lipoprotein (LDL) levels, and low high-density lipoprotein (HDL) levels.
- Endocrine factors
- Race, sex, and age factors
- Ethnic and cultural factors
- Socioeconomic status
- Dietary habits
- Smoking cessation
- Pregnancy and menopause
- Psychological factors
- History of gestational diabetes
- Lactation history in mothers

Genetic susceptibility loci. Rarely, obesity may be caused by a single gene, but much more commonly it is a complex interplay of susceptibility loci and environmental factors. Genome-wide association studies (GWAS) have found a robust number of genetic susceptibility loci associated with obesity. A single-nucleotide polymorphism (SNP) in the *FTO* (fat mass and obesity associated) gene and SNPs near the *MC4R* (melanocortin 4 receptor) gene have been highly associated with BMI.

More than 90% of human cases of obesity are thought to be multifactorial. Nevertheless, the recognition of monogenic variants has greatly enhanced knowledge of the etiopathogenesis of obesity [15].

POMC and MC4. Proopiomelanocortin (POMC) is converted into alpha–melanocyte-stimulating hormone (alpha-MSH), which acts centrally on the melanocortin receptor 4 (MC4) to reduce dietary intake. Genetic defects in POMC production and mutations in the *MC4* gene are described as monogenic causes of obesity in humans [16].

Of particular interest is the fact that patients with *POMC* mutations tend to have red hair because of the resultant deficiency in MSH production. Also, because of their diminished levels of adrenocorticotropic hormone (ACTH), they tend to have central adrenal insufficiency.

Data suggest that up to 5% of children who are morbidly obese have *MC4* or *POMC* mutations [16]. If confirmed, these would be the most common identifiable genetic defects associated with obesity in humans (band 2p23 for *POMC* and band 18q21.3 for *MC4*).

Leptin deficiency. Rare cases of humans with congenital leptin deficiency caused by mutations in the leptin gene have been identified (the involved band is at 7q31.) The disorder is autosomal recessive and manifested by severe obesity and hyperphagia accompanied by metabolic, neuroendocrine, and immune dysfunction. It is exquisitely sensitive to leptin injection, with reduced dietary intake and profound weight loss.

Convertase mutation. Prohormone convertase, an enzyme that is critical in protein processing, appears to be involved in the conversion of POMC to alpha-MSH. Rare patients with alterations in this enzyme have had clinically significant obesity, hypogonadotropic hypogonadism, and central adrenal insufficiency. This is one of the few models of obesity not associated with insulin resistance.

PPAR-gamma is a transcription factor that is involved in adipocyte differentiation. All humans with mutations of the receptor (at band 3p25) described so far have had severe obesity.

Inflammatory factors. Evolving data suggest that a notable inflammatory, and possibly infective, etiology may exist for obesity. Adipose tissue is known to be a repository of various cytokines, especially interleukin-6 and tumor necrosis factor alpha.

Data have shown that adenovirus-36 infection is associated with obesity in chickens and mice. In human studies, the prevalence of adenovirus-36 infection is 20-30% in people who are obese, versus 5% in people who are not obese. Despite these provocative findings, the roles of infection and inflammation in the pathogenesis of obesity remain unclear.

Epidemiology. The prevalence of obesity worldwide is increasing, particularly in the industrialized nations of the Northern hemisphere, such as the US, Canada, and most countries of Europe. Approximately 78 million adults above age 20 (37.5 million men and 40.6 million women) and 12.5 million children and adolescents (5.5 million boys and 7 million girls) in the US are obese. In 2009-2010, the prevalence of obesity among men and women was almost 36% [1]. The prevalence in children and adolescents was 16.9% [1]. Approximately 20-25% of children are either overweight or obese, and the prevalence is even greater in some minority groups, including Pima Indians, Mexican Americans, and African Americans [17].

During the past several decades, the prevalence of obesity and overweight has increased sharply for adults in the US: among adults aged 20-74 years, the prevalence of obesity increased from 15% in the 1976-1980 survey to 32.9% in the 2003-2004 survey. Data from the past few years, however, indicate a potential stabilization of obesity trends in adults and children [1].

Overweight and obesity were associated with nearly 1 in 5 deaths (18.2%) among adults in the US from 1986 through 2006 [17].

Obesity appeared to have a particularly strong effect among black women, with 26.8% of deaths associated with a BMI of 25 kg/m^2 or higher [17]. In white women, 21.7% of deaths were associated with overweight or obesity. Among black men, 5.0% of deaths were associated with overweight or obesity, and among white

men, 15.6% were. Data also show the more recent the birth year, the greater effect obesity has on mortality rates [17].

Reports from countries such as Malaysia, Japan, Australia, New Zealand, and China have detailed an epidemic of obesity in the past 2-3 decades. Data from the Middle Eastern countries of Bahrain, Saudi Arabia, Egypt, Jordan, Tunisia, and Lebanon, among others, indicate this same disturbing trend, with levels of obesity often exceeding 40%.

Internationally, rates of obesity are higher in women than in men. A somewhat higher rate would be expected, given the biologically higher percentage of body fat in women.

Information from the Caribbean and from South America highlights similar trends. Although data from Africa are scant, a clear and distinct secular trend of profoundly increased BMIs is observed when people from Africa emigrate to the northwestern regions of the world. Comparisons of these indices among Nigerians and Ghanaians residing in their native countries with indices in recent immigrants to the US show this trend poignantly.

Conservative estimates suggest that as many as 250 million people (approximately 7% of the estimated current world population) are obese. Two to 3 times more people than this are probably overweight. Although socioeconomic class and the prevalence of obesity are negatively correlated in most industrialized countries, including the US, this correlation is distinctly reversed in many relatively undeveloped areas, including China, Malaysia, parts of South America, and sub-Saharan Africa.

Race-related demographics. Obesity is a cosmopolitan disease that affects all races worldwide. However, certain ethnic and racial groups appear to be particularly predisposed. The Pima Indians of Arizona and other ethnic groups native to North America have a particularly high prevalence of obesity. In addition, Pacific islanders (eg, Polynesians, Micronesians, Maoris), African Americans, and Hispanic populations (either Mexican or Puerto Rican in origin) in North America also have particularly high predispositions to the development of obesity.

Secular trends clearly emphasize the importance of environmental factors (particularly dietary issues) in the development of obesity. In many genetically similar cohorts of high-risk ethnic and racial groups, the prevalence of obesity in their countries of origin is low but rises considerably when members of these groups emigrate to the affluent countries of the Northern Hemisphere, where they alter their dietary habits and activities.

Age-related demographics. Children, particularly adolescents, who are obese have a high probability of becoming adults who are obese; hence, the bimodal distribution of obesity portends a large-scale obesity epidemic in the next few decades. Taller children generally tend to be more obese than shorter peers, are more insulin-resistant, and have increased leptin levels [18].

Adolescent obesity poses a serious risk for severe obesity during early adulthood, particularly in non-Hispanic black women. This calls for a stronger emphasis on weight reduction during early adolescence, specifically targeting groups at greater risk.

Prognosis. Data from insurance databases and large, prospective cohorts, such as findings from the Framingham and NHANES studies, clearly indicate that obesity is associated with a substantial increase in morbidity and mortality rates.

The adverse consequences of obesity may be attributed in part to comorbidities, but results from several observational studies detailed by the Expert Panel on the Identification.

For a person with a BMI of 25-28.9 kg/m^2, the relative risk for coronary heart disease is 1.72. The risk progressively increases with an increasing BMI; with BMIs greater than 33 kg/m^2, the relative risk is 3.44. Similar trends have been demonstrated in the relationship between obesity and stroke or chronic heart failure.

Overall, obesity is estimated to increase the cardiovascular mortality rate 4-fold and the cancer-related mortality rate 2-fold [2]. As a group, people who are severely obese have a 6- to 12-fold increase in the all-cause mortality rate. Although the exact magnitude of the attributable excess in mortality associated

with obesity (about 112,000-365,000 excess deaths annually) has been disputed, obesity is indisputably the greatest preventable health-related cause of mortality after cigarette smoking.

For persons with severe obesity (BMI ≥40), life expectancy is reduced by as much as 20 years in men and by about 5 years in women. The greater reduction in life expectancy for men is consistent with the higher prevalence of android (ie, predominantly abdominal) obesity and the biologically higher percent body fat in women. The risk of premature mortality is even greater in obese persons who smoke.

Some evidence suggests that, if unchecked, trends in obesity in the US may be associated with overall reduced longevity of the population in the near future. Data also show that obesity is associated with an increased risk and duration of lifetime disability. Furthermore, obesity in middle age is associated with poor indices of quality of life in old age.

The mortality data appear to have a *U*- or *J*-shaped conformation in relation to weight distribution [19].

The degree of obesity (generally indicated by the BMI) at which mortality discernibly increases in African Americans and Hispanic Americans is greater than in white Americans; this observation suggests a notable racial spectrum and difference in this effect. The optimal BMI in terms of life expectancy is about 23-25 for whites and 23-30 for blacks. Emerging data suggest that the ideal BMI for Asians is substantially lower than that for whites.

The individuals who have abdominal obesity (elevated waist circumference) are at risk for obesity-related health complications. Most individuals with a BMI of over 25 and essentially all persons with a BMI of more than 30 have abdominal obesity.

Factors that modulate the morbidity and mortality associated with obesity include the following:

- Age of onset and duration of obesity
- Severity of obesity

- Amount of central adiposity
- Comorbidities
- Gender
- Level of cardiorespiratory fitness
- Race

Morbidity in elderly persons. A longitudinal study by Stessman et al of more than 1000 individuals indicated that a normal BMI, rather than obesity, is associated with a higher mortality rate in elderly people [20].The investigators determined that a unit increase in BMI in female members of the cohort could be linked to hazard ratios (HRs) of 0.94 at age 70 years, 0.95 at age 78 years, and 0.91 at age 85 years.

In men, a unit increase in BMI was associated with HRs of 0.99 at age 70 years, 0.94 at age 78 years, and 0.91 at age 85 years. According to a time-dependent analysis of 450 cohort members followed from age 70 to age 88 years, a unit increase in BMI produced an HR of 0.93 in women and in men. [74]

Weight-loss programs

Most individuals are able to attain weight loss in the short term, but weight regain is unfortunately a common pattern. On average, participants in nonsurgical weight-management programs lose approximately 10% of their initial body weight over 12-24 weeks, but the majority regained two thirds of the weight lost within a year.

Old data indicated that 90-95% of the weight lost is regained in 5 years. Recent data show that more intensive and structured nonsurgical weight management may help a significant number of patients to maintain most of the weight lost for up to 4 years.

Patient Education. In studies among low-income families, adults and adolescents noted caloric information when reading labels. However, this information did not affect food selection by adolescents or parental food selections for children.

The patients who received a formal diagnosis of overweight/obese from a healthcare provider demonstrated a higher rate of dietary change and/or physical activity than did persons whose overweight/obese condition remained undiagnosed.

The child obesity prevention programs have beneficial effects.

History. In most patients, the presentation of obesity is straightforward, with the patient indicating problems with weight or repeated failure in achieving sustained weight loss. In other cases, however, the patient may present with complications and/or associations of obesity.

A full history must include a dietary inventory and an analysis of the patient’s activity level. Screening questions to exclude severe or untreated depression are vital because depression may be a consequence or a cause of excessive dietary intake and reduced activity.

Because almost 30% of patients who are obese have eating disorders, screen for these in the history. The possibility of bingeing, purging, lack of satiety, food-seeking behavior, night-eating syndrome, and other abnormal feeding habits must be identified because management of these habits is crucial to the success of any weight-management program.

When taking the history, the clinician should investigate whether other members of the patient's family have weight problems, inquire about the patient's expectations, and estimate the patient's level of motivation. The clinician should also determine whether the patient has had any of the comorbidities related to obesity, including the following [1].

- Respiratory: Obstructive sleep apnea, greater predisposition to respiratory infections, increased incidence of bronchial asthma, and Pickwickian syndrome (obesity hypoventilation syndrome)
- Malignant: Association with endometrial (premenopausal), prostate, colon (in men), rectal (in men), breast (postmenopausal), gall bladder, gastric cardial, biliary tract system, pancreatic, ovarian, renal, and possibly lung cancer, as well as esophageal adenocarcinoma and multiple myeloma [2].

- Psychological: Social stigmatization and depression
- Cardiovascular: Coronary artery disease, essential hypertension, left ventricular hypertrophy, cor pulmonale, obesity-associated cardiomyopathy, accelerated atherosclerosis, and pulmonary hypertension of obesity
- Central nervous system (CNS): Stroke, idiopathic intracranial hypertension, and meralgia paresthetica
- Obstetric and perinatal: Pregnancy-related hypertension, fetal macrosomia, and pelvic dystocia
- Surgical: Increased surgical risk and postoperative complications, including wound infection, postoperative pneumonia, deep venous thrombosis, and pulmonary embolism
- Pelvic: Stress incontinence
- Gastrointestinal (GI): Gall bladder disease (cholecystitis, cholelithiasis), nonalcoholic steatohepatitis (NASH), fatty liver infiltration, and reflux esophagitis
- Orthopedic: Osteoarthritis, coxa vera, slipped capital femoral epiphyses, Blount disease and Legg-Calvé-Perthes disease, and chronic lumbago
- Metabolic: Type 2 diabetes mellitus, prediabetes, metabolic syndrome, and dyslipidemia
- Reproductive: In women: Anovulation, early puberty, infertility, hyperandrogenism, and polycystic ovaries; in men: hypogonadotropic hypogonadism
- Cutaneous: Intertrigo (bacterial and/or fungal), acanthosis nigricans, hirsutism, and increased risk for cellulitis and carbuncles
- Extremity: Venous varicosities, lower extremity venous and/or lymphatic edema
- Miscellaneous: Reduced mobility and difficulty maintaining personal hygiene

Include questions to exclude secondary causes of obesity, some of which are rare.

Figure 2

Secondary Causes of Obesity

1. Hypothyroidism
2. Cushing's syndrome
3. Insulinoma
4. Hypothalamic obesity
5. Polycystic ovarian syndrome
6. Genetic syndromes such as Prader Willi, Alstroms, Bardet Biedl, Cohens, Borjeson Forsmsman Lehmann and Frohlich's syndrome
7. Growth hormone deficiency
8. Oral contraceptive use
9. Pregnancy
10. Medication related: including phenothiazines, sodium valproate, carbamazepine, tricyclic antidepressants, lithium, glucocorticoids, megesterol acetate, the thiazolidine diones, the sulphonylureas, insulin, adrenergic antagonists, serotonin anatagonists especially cyproheptadine.
11. Smoking cessation
12. Eating disorders: especially binge eating disorder, bulimia nervosa and night eating disorder
13. Hypogonadism
14. Pseudohypoparathyroidism
15. Tube feeding related obesity

Physical Examination. In the clinical examination, measure anthropometric parameters and perform the standard, detailed examination required in evaluating patients with any chronic, multisystem disorder, such as obesity.

Waist and hip circumference are useful surrogates in estimating visceral fat; serial tracking of these measurements helps in estimating the clinical risk over time. Neck circumference is predictive of a risk of sleep apnea, and its serial measurement in the individual patient is clinically useful for risk stratification.

Examination of organ systems should include the following:

- Cutaneous - Search for intertriginous rashes from skin-on-skin friction; also search for hirsutism in women, acanthosis nigricans, and skin tags, which are common with insulin resistance secondary to obesity
- Cardiac and respiratory - Exclude cardiomegaly and respiratory insufficiency

- Abdominal - Attempt to exclude tender hepatomegaly, which may suggest hepatic fatty infiltration or NASH, and distinguish the striae distensae from the pink and broad striae that suggest cortisol excess

When examining the extremities, search for joint deformities (eg, coxa vara), evidence of osteoarthritis, and any pressure ulcerations. Localized and lipodystrophic fat distribution should also be identified, because of their common association with insulin resistance.

Diagnostic Considerations. Mesomorphic body states, as seen in bodybuilders and people in related occupations (eg, professional wrestling), may be associated with elevated BMIs, but as a result of increased muscle mass rather than excess adiposity. In addition, anasarca may be mistaken for obesity if not carefully evaluated clinically. Other conditions to consider while examining for obesity include the following:

- Depression
- Type 2 diabetes mellitus
- Fatty liver
- Gastroesophageal reflux disease (GERD)
- Hirsutism
- Polygenic hypercholesterolemia
- Hypothyroidism
- Insulinoma
- Kallmann syndrome and idiopathic hypogonadotropic hypogonadism
- Generalized lipodystrophy
- Polycystic ovarian disease (Stein-Leventhal syndrome)
- Cushing syndrome
- Adiposa dolorosa (Dercum disease)
- Partial lipodystrophies associated with localized lipohypertrophy

Differential Diagnoses

- Acromegaly
- Ascites

- Iatrogenic Cushing Syndrome

Approach Considerations. Standard laboratory studies in the evaluation of obesity should include the following:

- Fasting lipid panel: test fasting cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) levels. These levels may be normal, or the typical dyslipidemia associated with cardiometabolic syndrome may be found. This dyslipidemia is characterized by reduced HDL-C and elevated fasting triglyceride concentrations; however, increased low-density lipoprotein cholesterol (LDL-C) and normal to marginally increased total cholesterol are not uncommon among obese individuals.
- Liver function studies: normal results in most obese patients. However, elevated transaminase levels may indicate nonalcoholic steatohepatitis (NASH) or fatty infiltration of the liver).
- Thyroid function tests: typically normal, but checking them to detect primary hypothyroidism (characterized by increased serum thyrotropin and normal or reduced thyroxine and/or triiodothyronine levels) is worthwhile. Screening with a serum thyrotropin level is usually sufficient. Of importance, hypothyroidism itself rarely causes more than mild obesity.
- Fasting glucose and hemoglobin A1c (HbA1c): obesity is associated with insulin resistance and increased serum levels of fasting insulin and C-peptide serum levels. However, insulin levels are normal in many persons who are obese. All patients with obesity should be screened for diabetes. Additional information is gained by using glucose and HbA1c tests together if the patient is fasting. Prediabetes is indicated by impaired fasting glucose (fasting plasma glucose levels of 100-125 mg/dL [5.6-6.9 mmol/L]) or impaired glucose tolerance (2-h oral glucose tolerance test values of 140-199 mg/dL [7.8-11.0 mmol/L]). Patients with these findings are at relatively high risk for the future development of diabetes. Type 2 diabetes is diagnosed when the fasting glucose is 126 mg/dL or greater or HbA1c is 6.5% or higher [21].

Other tests are performed as indicated by clinical findings. For example, the 24-hour urinary free-cortisol test is needed only when Cushing syndrome or other hypercortisolemic states are clinically suspected. However, approximately 4% of patients with Cushing syndrome have normal urinary free-cortisol values.

Evaluation of Degree of Fat

Body mass index (BMI) calculation, waist circumference, and waist/hip ratio are the common measures of the degree of body fat used in routine clinical practice. Other procedures that are used in few clinical centers include the following:

- Caliper-derived measurements of skin-fold thickness
- Dual-energy radiographic absorptiometry (DEXA)
- Bioelectrical impedance analysis
- Ultrasonography to determine fat thickness
- Underwater weighing

The standard techniques for measuring visceral fat are magnetic resonance imaging (MRI) and computed tomography (CT) scanning. Less expensive techniques for direct measurement of visceral fat include abdominal ultrasonography and abdominal bioelectrical impedance.

Approach Considerations. Treatment of obesity starts with comprehensive lifestyle management (ie, diet, physical activity, behavior modification), which should include the following [3]:

- Self-monitoring of caloric intake and physical activity
- Goal setting
- Stimulus control
- Nonfood rewards
- Relapse prevention

As with all chronic medical conditions, effective management of obesity must be based on a partnership between a highly motivated patient and a committed team of health professionals. This team may include the physician, a psychologist or psychiatrist, physical and exercise therapists, dietitians, and other

subspecialists, depending on the comorbidities of the individual patient. Scientific evidence indicates that multidisciplinary programs reliably produce and sustain modest weight loss between 5% and 10% for the long-term [22].

The Endocrine Society released guidelines on the treatment of obesity to include the following [23]:

- Diet, exercise, and behavioral modification should be included in all obesity management approaches for body mass index (BMI) of 25 kg/m^2 or higher. Other tools, such as pharmacotherapy for BMI of 27 kg/m^2 or higher with comorbidity or BMI over 30 kg/m^2 and bariatric surgery for BMI of 35 kg/m^2 with comorbidity or BMI over 40 kg/m^2 , should be used as adjuncts to behavioral modification to reduce food intake and increase physical activity when this is possible.
- Drugs may amplify adherence to behavior change and may improve physical functioning such that increased physical activity is easier in those who cannot exercise initially. Patients who have a history of being unable to successfully lose and maintain weight and who meet label indications are candidates for weight loss medications.
- To promote long-term weight maintenance, the use of approved weight loss medication (over no pharmacological therapy) is suggested to ameliorate comorbidities and amplify adherence to behavior changes, which may improve physical functioning and allow for greater physical activity in individuals with a BMI of 30 kg/m^2 or higher or in individuals with a BME of 27 kg/m^2 and at least one associated comorbid medical condition (eg, hypertension, dyslipidemia, type 2 diabetes mellitus, and obstructive sleep apnea).
- If a patient's response to a weight loss medication is deemed effective (weight loss of 5% or more of body weight at 3 mo) and safe, it is recommended that the medication be continued. If deemed ineffective (weight loss less than 5% at 3 mo) or if there are safety or tolerability issues at any time, it is recommended that the medication be discontinued and alternative medications or referral for alternative treatment approaches be considered.

- In patients with type 2 diabetes mellitus who are overweight or obese, antidiabetic medications that have additional actions to promote weight loss (such as glucagon-like peptide-1 [GLP-1] analogs or sodium-glucose-linked transporter-2 [SGLT-2] inhibitors) are suggested, in addition to the first-line agent for type 2 diabetes mellitus and obesity, metformin.
- In obese patients with type 2 diabetes mellitus who require insulin therapy, at least one of the following is suggested: metformin, pramlintide, or GLP-1 agonists to mitigate associated weight gain due to insulin. The first-line insulin for this type of patient should be basal insulin. This is preferable to using either insulin alone or insulin with sulfonylurea.
- Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers, rather than beta-adrenergic blockers, should be considered as first-line therapy for hypertension in patients with type 2 diabetes mellitus who are obese.
- In women with a BMI of 27 kg/m^2 or more with comorbidities or a BMI of 30 kg/m^2 or more, seeking contraception, oral contraceptives are suggested over injectable medications because of weight gain with injectables, provided that women are well informed about the risks and benefits (ie, oral contraceptives are not contraindicated).

Weight-loss programs. The 3 major phases of any successful weight-loss program are as follows:

- Preinclusion screening phase
- Weight-loss phase
- Maintenance phase - This can conceivably last for the rest of the patient's life but ideally lasts for at least 1 year after the weight-loss program has been completed.

Evidence supports the use of commercial weight-loss programs. A 12-week randomized, controlled trial found that commercially available weight-loss programs are more successful and more affordable than primary care practice–based programs led by specially trained staff.

Patient Screening, Assessment, and Expectations

Before enrolling any patient in a weight-loss program, the clinician must have a clear idea of that individual's expectations. A patient with unrealistic expectations should not be enrolled until these are changed to realistic and attainable goals. The clinician should guide the patient who seeks weight reduction to create goals that fit the mnemonic SMART: Specific, Measurable, Attainable, Realistic, and Timely.

A specific goal has a much greater chance of being accomplished than a general goal does. To set a specific goal, the patient must answer the following $6W$ questions:

- Who - Who is involved?
- What - What do I want to accomplish?
- Where - Identify a location
- When - Establish a time frame
- Which - Identify requirements and constraints
- Why - Identify specific reasons for or purpose or benefits of the goal

Also crucial is a clear assessment of the patient's level of motivation regarding the changes in diet, exercise, and behavior required to maintain weight loss. This assessment should be completed before the patient is enrolled in a weight-loss program.

Comprehensive, written, informed consent must be obtained and should address details of the expected weight loss and the required changes. Clinical judgment may support a less stringent approach in some situations.

Psychiatric comorbidities. Because of the potential harm of attempting weight loss in an unsuitable candidate, all patients to be enrolled in any surgical, medical, or other weight-loss program should be screened for serious mental illness (eg, severe or untreated depression) and for eating disorders.

Many of the psychological and psychiatric problems commonly associated with obesity are not contraindications to enrollment in a weight-loss program; for example, mild to moderate depression typically improves with weight loss.

Nevertheless, clinicians and patients must be aware of these problems before enrollment. In addition, the clinician must ensure that any such problems are relatively stable, quiescent, or well managed before the patient begins a weight-loss program.

Weight-Loss Goals. In general, body weight and body fat are tenaciously regulated. This underlies the challenge of weight loss and highlights the importance of setting realistic weight-loss goals. Recognition of this challenge, and of the value of modest weight loss, have led to a paradigm shift in the medical management of obesity from a goal of massive weight loss to one of maintaining the highest weight possible while still eliminating obesity-related comorbidities or reducing them to a minimum.

Available data suggest that a loss of approximately 10% of body weight in persons who are obese (BMI <40 kg/m^2) is associated with substantial health benefits regarding obesity-related comorbidities [24]. However, according to guidelines released by the American College of Cardiology (ACC), the American Heart Association (AHA), and The Obesity Society (TOS) in 2013, clinically meaningful health improvements can even be seen with weight loss in the range of 2-5% [22].

A reasonable goal for weight loss in the setting of a medical treatment program is approximately 1-2 lb/wk. However, it is becoming increasingly apparent that the weight-loss goal for each patient must be individualized and cannot be unilaterally based on standard weight-for-height norms.

In addition to the patient's weight, factors to consider when setting individualized weight loss goals are the weight of other family members, as well as the patient's cultural, ethnic, and racial background.

Weight-Loss Maintenance. Evidence from the National Weight Control Registry (NWCR), which tracks indices and predictors in individuals who have lost at least 30 pounds and have maintained that loss for at least 1 year, suggests that patterns associated with successful weight maintenance include the following:

- Self-monitoring of weight

- Consumption of a low-fat diet
- Daily physical activity of approximately 60 minutes
- Minimal sedentary “screen time”
- Consumption of most meals at home

Although some data from randomized trials of diets of different macronutrient composition indicate that caloric restriction, self-monitoring, and program attendance are more important than any specific composition of dietary macronutrient, results from a large European study indicated that weight-loss maintenance is better achieved with a diet modestly high in protein with lower glycemic index comparison to other macronutrient compositions [25].

The patients regaining weight after initial weight loss on long-term dietary intervention nevertheless continued to show long-lasting improvements in high-sensitivity C-reactive protein, adiponectin, fetuin, high-density lipoprotein cholesterol, progranulin, and vaspin. There are delayed effects following initial weight loss and/or continuous beneficial effects from switching to a healthier diet [25].

Diet-induced weight loss can result in elevated levels of hormones that increase appetite. After successful weight loss, circulating levels of these hormones do not decrease to levels recorded before diet-induced weight loss. Thus, long-term strategies are needed to prevent obesity relapse [26].

Contrary to the original belief, however, weight loss after nonsurgical intervention can be maintained long-term. The patients with diabetes and obesity can maintain an average of 6.4% weight loss after 5 years of intensive lifestyle changes in real-world clinical practice. This study also found that patients who maintain 7% or greater weight loss after a year are more likely to maintain weight loss over the long-term [25].

Treatment of Childhood Obesity

In cases of childhood obesity [27], the goal is not to cause weight loss, but to reduce the rate of weight gain to fit normal growth curves. The basic principles of management include the following:

- Modifying diet
- Increasing appropriate physical activity and exercise
- Reducing time spent in sedentary activities - Eg, watching television
- Modifying behavior

Medication therapy may also be used in the management of pediatric obesity, but close monitoring and a combination of all the aforementioned modalities is required to achieve substantial and sustained weight loss. At the present, orlistat is the only medication approved by the US Food and Drug Administration (FDA) for use as an adjunct for weight loss in adolescents.

Energy Expenditure and Weight Loss. Achieving a caloric deficit is still the most important component in achieving sustained weight loss. However, the considerable variance in individual energy expenditures and compliance with calorie-deficient plans make it difficult to reliably predict how much weight an individual will lose.

Among the caveats is the fact that energy expenditure is related to body weight; about 22 kcal/kg of energy is required for basal maintenance of 1 kg of weight in a typical adult. Therefore, weight loss tends to reduce energy expenditure, dampening the effect of caloric deficits.

Because of their lowered energy expenditure, older subjects have increased difficulty in achieving sustained weight loss. The estimated reduction in energy expenditure is 100 kcal per decade after the age of 30 years. Presumably because of their greater lean mass proportions, men tend to lose more weight than women do when caloric deficits are similar [22].

Conventional Diets can be broadly classified into 2 categories: balanced, low-calorie diets (or reduced portion sizes) and diets with different macronutrient compositions. The latter include the following:

- Low-fat diets - Eg, the Ornish diet
- Low-carbohydrate diets - Eg, the Atkins diet

- Midlevel diets - Eg, the Zone diet, in which the 3 major macronutrients (fat, carbohydrate, protein) are eaten in similar proportions of 30-40%)
- Joslin Why WAIT diet for diabetic patients - 40-45% carbohydrates, 20-30% protein, less than 35% fat

Reduced - portion size diets and balanced, low-calorie diets. Balanced, low-calorie diets and reduced - portion size diets are the types that dietitians and other weight-management professionals most commonly prescribe. Although these diets are useful for short-term weight loss, none of them alone is associated with reliable, sustained weight loss.

These diets underlie most of the popular, commercial weight-loss programs. The basic premise for people on these diets involves obtaining their detailed dietary inventory and using it to estimate their mean daily caloric intake.

A reasonable goal for the caloric deficit is based on the new goal for total daily calories. Meal plans are then devised to provide this total, divided among 3 or more meals throughout the day.

Reduced - portion size diets. The meals may be based on regular, everyday foods. The strategies for effective reduction of portion sizes become central.

Alternatively, portion control can be achieved by participation in structured weight loss programs (eg, Jenny Craig, Nutrisystem) or by the purchase of products such as meal-replacement shakes, bars, prepackaged meals, and frozen entrees (eg, Slim-Fast, Glucerna, Lean Cuisine, Healthy Choice, Smart Ones). These have adequate amounts of the major macronutrients based on the food pyramid from the US Department of Agriculture and recommended daily allowances (RDAs). These sources also have adequate micronutrients and trace elements.

Alcohol, sodas, most fruit juices, and highly concentrated sweets are generally calorie dense and nutrient deficient (so-called empty calories). Consequently, these are generally prohibited or reduced to a minimum.

Low-calorie diets involve reducing daily caloric intake by 500-1000 kcal/day, to a level of 800-1800 kcal/day. These diets are associated with a mean weight loss of 0.4-0.5 kg per week (1-2 lb/wk). In ideal settings, total loss can be 5-10% of starting weight (10-20 lb for a 200-lb person) over 3-6 months, occasionally higher if the individual is very successful.

With any low-calorie diet, maintaining an intake of protein with a high biologic value of 1-1.5 g/kg of adjusted body weight (adjusted body weight = ideal body weight + one quarter of the excess weight) is vital to preserve lean body mass. Reducing intake to less than 1200 kcal/day while keeping the percentage protein at 15% may lead to protein malnutrition and significant muscle mass loss. For example, for a person following a 1200 calorie diet and aiming to consume 25% protein, the goal should be 300 kcal/day of protein (75 g).

Major potential complications to watch for include the following:

- Vitamin deficiency
- Starvation ketosis
- Electrolyte derangements
- Cholelithiasis

Diets with different macronutrient compositions involve a caloric intake of greater than 1200 kcal/day. This type of diet is designed to reduce the caloric intake by 500-1000 kcal/day from the patient's current dietary intake.

The suggested composition used by the best-validated dietary programs is as follows:

- Protein intake of 0.8-1.5 g/kg of body weight (not to exceed 100 g/day)
- 10-30% of total calories from fat (preferably ≥90% as polyunsaturated fat and < 10% as saturated fat)
- Carbohydrate intake of 50 g/day or more
- Water intake of 1 L or more
- Adequate micronutrients and macronutrients based on the RDAs

Low-carbohydrate diets have become popular in the past few decades, with the Atkins diet being the most popular. The Atkins diet is a high-protein and/or high-fat, very-low-carbohydrate diet that induces ketosis. The very-low-carbohydrate content is critical in inducing short-term weight loss in the first 2-4 weeks; this is largely the result of fluid mobilization.

Ketone bodies tend to be generated when an individual's daily dietary carbohydrate intake is under 50 g, and sodium diuresis is forced, causing most of the short-term weight loss. No robust data about the safety or long-term effectiveness of this diet are available.

The premise of the diet is that caloric intake as protein is less prone to fat storage than is the equivalent caloric intake as carbohydrate; however, no physiologic data support this premise. Owing to the high fat content of such diets, low-density lipoprotein cholesterol (LDL-C) levels were found to be increased by at least 10% in 25% of patients who used this diet.

Data on the long-term effects of a high-protein diet in rodents cause concern. They indicate that these diets may be associated with a reduced life span and a predisposition to neoplasia.

The South Beach diet is another low-carbohydrate diet. This program is more liberal in its carbohydrate allowance than the Atkins diet. In addition, the South Beach diet distinguishes between what are considered to be good and bad carbohydrates on the basis of their glycemic index.

Although the relevance and importance of the glycemic index is controversial, the diet encourages increased fiber intake, which is associated with lowered weight even when total caloric intake is relatively unchanged. Low glycemic index diets are better at helping to maintain weight loss than diets with a higher glycemic index; the same is true of diets with modestly increased protein intake, versus standard protein intake [25].

Persons who decide to use a low-carbohydrate diet should choose heart-healthy sources of fat, including monounsaturated fats, polyunsaturated fats, and

fats rich in omega-3 fatty acids, rather than saturated fat. Protein sources should be fish, nuts, legumes, and lean poultry rather than pork chops, steak, and mutton.

Comparison of diet programs

Dansinger and colleagues compared the Zone, Ornish, and Atkins diets to each other and to a typical balanced, calorie-restricted (Weight Watchers) diet and found them all to have a similar impact on weight [28]. The Ornish diet (a very low-fat diet) and the Atkins diet had the poorest compliance rates. At 1 year, the researchers observed no significant differences in weight loss among the 4 diets. Compliance and caloric deficits were more important predictors of weight loss and improvement in cardiovascular risk surrogates than was specific dietary composition.

The low-carbohydrate and low-fat diets are equally efficacious in inducing weight loss. However, a low-carbohydrate diet is associated with favorable changes in cardiovascular disease risk factors [28]. Nevertheless, better achievement of sustained weight loss is seen with low-fat diets than with low-carbohydrate diets, probably because of generally higher compliance.

Very-Low-Calorie Diets (VLCDs) are best used in an established, comprehensive program. VLCDs involve reducing caloric intake to 800 kcal/day or less. When used in optimal settings, they can achieve a weight loss of 1.5-2.5 kg/wk (3.3-5.5 lb/wk), with a total loss of as much as 20 kg over 12 weeks. No good-quality evidence suggests that a daily calorie intake of less than 800 kcal/day achieves any additional weight loss in the long-term [28].

VLCDs are associated with profound initial weight loss, much of which is from loss of lean mass in the first few weeks. This loss rapidly ceases, and weight-loss velocity then flattens. Such rapid weight loss is frequently followed with weight regain due to reduction in basal energy expenditure secondary to the loss of fat free mass.

Use special caution whenever VLCDs are prescribed to children, adolescents, or elderly patients. Use of VLCDs is contraindicated in the following settings:

- Pregnancy
- Protein-wasting states
- Clinically significant cardiac, renal, hepatic, psychiatric, or cerebrovascular disease
- Any other chronic disease

Although VLCDs are associated with notable short-term weight loss and improved blood pressure and glycemic control, they cannot be sustained for longer than 3-6 months. Compliance beyond a few weeks is poor, and close supervision is required to avoid mishaps.

Among the major complications to monitor are hair loss, skin thinning, hypothermia, cholelithiasis, and electrolyte derangement. VLCDs have little or no utility in long-term weight management and are probably best used as stopgap measures before bariatric surgery or a long-term, comprehensive weight-loss program in patients with very severe or morbid obesity and associated comorbidities (BMI ≥50).

Preoperative VLCDs have been postulated to decrease surgical risk by enhancing visualization during laparoscopic bariatric surgery. The surgeons' perceptions of the procedure's difficulty were lower in the VLCD patients.

Water Drinking. It was found that in overweight and obese middle-aged and older adults on a hypocaloric diet, drinking 500 mL of water before each main meal aided weight loss. Water drinking could assist weight loss in overweight children. Drinking 10 mL/kg of cold water could result in an additional weight loss of about 1.2 kg/y. This is achieved primarily through a water-induced increase in resting energy expenditur.

Exercise Programs

Before prescribing an intensive exercise program, clinicians should screen patients for cardiovascular and respiratory adequacy. Any clinically significant anomalies found require full evaluation by appropriate specialist physicians, and only after these issues have been adequately managed and stabilized should the

patient begin an active exercise program. In contrast, patients starting a program of moderate exercise (eg, walking) do not require prescreening.

Aerobic isotonic exercise is of the greatest value for persons who are obese. The ultimate minimum goal should be to achieve 30-60 min of continuous aerobic exercise 5-7 times per week. Increased physical activity and exercise 300 min/week is associated with significant weight reduction and longer maintenance of the weight loss.

Anaerobic isometric exercise, including resistance training, can be cautiously added as an adjunct after the aerobic goal described above is achieved. Resistance training is valuable in minimizing muscle mass loss and is particularly beneficial in patients with diabetes, as it increases glucose uptake by muscles.

Since approximately 27% of the diet-induced weight loss is from loss of muscle, the addition of exercise to caloric restriction is important. Studies have shown that muscle mass loss is reduced to approximately 13% of the total weight loss when diet and exercise are combined [29].

Exercise also increases metabolic activity and reduces body fat. Although most patients may be unable to sustain enough regular exercise to achieve weight loss, consistent, moderate exercise is important in maintaining weight and in improving overall cardiorespiratory fitness [29]. Shorter bouts of exercise of around 10 minutes are associated with better adherence and more weight loss than are longer bouts of exercise.

The patients with severe obesity who introduced exercise concurrently with or after dietary intervention had significant weight loss and modification of cardiometabolic risk factors. Furthermore, the benefits of exercise in young age may translate into benefits beyond, particularly in young women [30]. This information is useful for patients and physicians who may be discouraged by the patients' initial inability to engage in exercise.

The community weight-loss and physical activity programs can have a positive impact on mobility in elderly people who are overweight or obese and are

in poor cardiovascular health [30]. In this study, participants with poorer mobility at baseline benefited the most from these interventions.

Behavioral Changes. Behavioral modification for weight loss addresses learned behaviors that contribute to excessive food intake, poor dietary choices or habits, and sedentary activity habits. Although this approach can yield improved results, it is inherently challenging and time-consuming.

Effecting behavioral change starts with taking a detailed inventory of the patient's daily activities, in order to identify activities, cues, circumstances, and practices that favor nonmeal eating and snacking. A trained professional must then have an in-depth discussion with the patient to develop an individualized plan to change these practices. The effectiveness of this modality depends on a highly motivated patient and a dedicated counselor who is willing to maintain long-term follow-up [31].

A sufficient amount of sleep favorably impacts the maintenance of fat-free mass during times of decreased energy intake. In contrast, insufficient sleep undermines the body's ability to limit expansion of fat mass. A healthy sleep pattern is therefore important to harness weight loss benefits from other interventions [32]. Seven to 8 hours of sleep are optimal. Shorter (< 6 h) or longer (>9 h) sleep duration is associated with increased total body weight. Treatment of obstructive sleep apnea, if present, also helps in weight reduction.

Antiobesity Medications. Few medications are available for the treatment of obesity. Examples of FDA-approved drugs that may be considered for the long-term treatment of obesity include orlistat, lorcaserin, the combinations of phentermine and extended-release topiramate, and the fixed-dose combination of bupropion and naltrexone. Generally, the medications approved by the US Food and FDA for obesity are intended for patients with a BMI of 30 kg/m^2 or more or of 27 kg/m^2 or more with a weight-related risk factor (eg, diabetes, hypertension). All are indicated as adjuncts to caloric restriction, increased physical activity, and behavior modification. Response to therapy should be evaluated by week 12. If a patient has not lost at least 5% of baseline body weight, stimulants should be

discontinued, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

The FDA has issued a consumer alert about over-the-counter weight-loss pills that contain undeclared, active pharmaceutical ingredients. These products, which are promoted and sold on Web sites and in retail stores, may be marketed as "dietary supplements". They have not been approved by the FDA, are illegal, and may be potentially harmful. In April 2015, the FDA banned the use of the amphetaminelike stimulant (BMPEA) in supplements (sometimes labeled as acacia rigidula) [33].

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PREVENTIVE ONCOLOGY

In many respects, cancer is a preventable disease. Estimates indicate that approximately one half of all cancer cases either arise from modifiable risk factors or can be detected as precursor lesions before the development of disease with metastatic potential [1].

Prevention of cancer can take place on several different levels:

- primary prevention addresses the cause of cancer so disease does not occur,
- secondary prevention identifies disease before the onset of symptoms and keeps it from becoming more extensive,
- tertiary prevention reduces complications and progression of disease once it has become clinically apparent.

Although cancer has overtaken cardiovascular disease to become the leading cause of death among men and women younger than 85 years in the US, and the number of cancer deaths continues to increase with the aging and growth of the population, age-standardized US death rates from cancer have been decreasing [2]. From 2001 to 2006, cancer mortality decreased over 1,5% per year. Overall cancer incidence has also decreased, by an average of 0,7% per year from 1999 to 2006 [3]. These declines have been attributed to risk reduction strategies, detection of early disease, and improvement in treatment strategies.

Risk Assessment

Assessment of an individual's risk is a key step in cancer prevention; risk assessment programs have been developed at many cancer centers to identify people who are at high risk. Review of personal and family medical history, work history, and lifestyle can help identify cancer risk factors, which may be modifiable (eg, tobacco use, sun exposure) or non-modifiable (eg, family history of cancer, sex, ethnicity, race, advancing age, hormone levels). Combinations of modifiable and non-modifiable risk factors place some people at particularly high risk for cancer.

Models of cancer risk have been developed to permit calculation of an individual's risk for a specific type of cancer. One of the best known of these is the Gail model, which predicts breast cancer risk on the basis of current age, race, age when menstruation began, age of first live birth, number of close relatives with breast cancer, number of breast biopsies, and the presence or absence of atypical hyperplasia on breast biopsies [3]. Like most cancer risk models, the Gail model has limitations: it does not include ovarian cancer history or breast cancer in second-degree relatives such as aunts, cousins, or grandparents. This model may also be less accurate in predicting risk in non-white women. Therefore, risk models should be selected based on each individual's situation in order to calculate risk as accurately as possible.

Overall, approximately 10% of cancers occur because of hereditary predisposition, such as mutations in cancer susceptibility genes (eg, *BHCA1* and *BRCA2*). Many of these mutations can be identified through analysis of a blood or tissue sample. Genetic testing is recommended only for individuals who have a personal or family history that is suggestive of an inherited cancer syndrome.

The survivors of childhood cancer are at excess risk of developing primary neoplasms later in life, with the greatest risk for digestive and genitourinary neoplasms in survivors older than 40 years [3].

Identification of the appropriate person for testing leads to more informative results for the entire family. In most cases, the person who has had the cancer that best fits the hereditary pattern should be chosen for testing. If a mutation is identified in this individual, others in the family who are at risk can then be tested for that specific mutation. Genetic analysis should always be preceded by careful genetic counseling, which continues after determination of gene mutation status. Identification of a genetic alteration may change recommendations for cancer screening, chemoprevention, and prophylactic surgery.

In addition to risk from genetic syndromes, it is estimated that approximately another 15-20% of cancers are familial, which may be due to low-

penetrance genetic changes or the effects of shared environment and behaviors. The remainder of cancers in the general population are considered sporadic.

Modifiable Risk Factors

Modifiable risk factors for cancer include tobacco use, sun exposure, diet, exercise, obesity, alcohol use, hormone replacement therapy (HRT), environmental/occupational exposures, infectious exposures, and sexual activity.

Tobacco use accounts for approximately one third of cancer deaths in the US [3]. Of these, lung cancer is the most common, but cancers of the blood, head and neck, esophagus, liver, pancreas, liver, stomach, cervix, kidney, colon, and bladder have also been linked to smoking. Many chemicals are present in tobacco smoke, including at least 69 known carcinogens [4]. Smokeless tobacco - chewing tobacco and dipping snuff - contains at least 28 carcinogens [5].

Smoking may also promote more aggressive forms of cancer: for example, tobacco use is associated with higher-grade and higher-stage prostate cancer. Secondhand smoke, also known as environmental tobacco smoke, has been associated with both lung and sinus cancers in nonsmokers. Considerable evidence indicates that smokeless tobacco and cigars also have deadly consequences, including lung, laryngeal, esophageal, and oral cancers [4, 5].

Carcinogenesis from tobacco use occurs through several mechanisms, including direct delivery of carcinogens to tissues, inflammation, and breakdown of physiologic barriers [4, 5]. Cessation of tobacco use has been shown to reduce both cancer-related and all-cause mortality. Health benefits start soon after quitting and can be seen even in long-time users. For former smokers who have been abstinent for 10 years, the risk of lung cancer is one half that of current smokers. This risk falls to as low as 10% for ex-smokers who have quit for 30 years or more. Moreover, the risk for cancers of the mouth, throat, and esophagus lessens significantly 5 years after quitting, and the risk of developing bladder or cervical cancers also decreases after just a few years of being nicotine free [4, 5].

Most individuals require several quit attempts before they are able to stop smoking. The addiction to tobacco use is both psychologic and biochemical.

Medications are available to address the biochemical aspects, whereas counseling and other social support are recommended for treating the psychologic aspects.

Nicotine replacement therapy provides nicotine without the other components of tobacco and can be administered through a patch, nasal spray, chewing gum, lozenge, or inhaler. The use of nicotine replacement doubles the rate of quitting tobacco use [4, 5].

The addition of bupropion, an antidepressant medication, may increase the efficacy of nicotine replacement. However, this medication should be avoided in individuals with a history of seizures or eating disorders.

The newest medication for smoking cessation is varenicline. Individuals with depression or other neuropsychiatric disorders should not take varenicline, as this medication may exacerbate their symptoms [4, 5].

Of course, the ideal way to reduce tobacco-associated cancers is for people to not start using tobacco in the first place.

Sun exposure. Nonmelanoma skin cancers comprise 40% of malignancies in the US. The incidence rates of melanoma, although much less common than nonmelanoma skin cancers is increasing and this condition has a much higher propensity for metastasis and death.

Ultraviolet radiation is a well-established carcinogen for both melanoma and nonmelanoma skin cancers. However, the patterns of sunlight exposure associated with these cancers differ significantly. Squamous cell carcinoma tends to occur in those who have chronic sun exposure, often due to occupational exposure from working outdoors [6].

Episodes of intense ultraviolet exposure, particularly in children and others without a history of chronic sun exposure, is associated with melanoma incidence, and a history of blistering sunburns more than doubles the risk of melanoma. Basal cell carcinoma, although usually associated with chronic sun exposure, has also been linked to intermittent exposure in a significant proportion of cases. In addition, the use of tanning beds has been associated with increased skin cancer

incidence; in fact, the WHO has recommended against the use of these devices for individuals younger than age 18 years [6].

Recent interest in vitamin D as a chemopreventive agent for several types of cancer has made sun avoidance a controversial topic, because this nutrient is most easily and effectively obtained from sun exposure. At this time, most groups recommend limiting exposure to the sun during peak hours (between 10 AM and 4 PM); using protective clothing, including hats and sunglasses; and using sunscreens with a sun protection factor (SPF) of 30 or greater. Sunscreens should be broad-spectrum and contain agents that work against both ultraviolet (UV) A and UVB radiation (eg, oxybenzone, avobenzone, titanium dioxide, or zinc oxide).

Proper use of sunscreen is also critical: regardless of the SPF, all sunscreen should be applied approximately 30 minutes before sun exposure and then reapplied liberally at least every 1,5-2 hours or after swimming or perspiring heavily. A randomized clinical trial demonstrated statistically significant protection against squamous cell carcinoma with regular use of sunscreen; however, it should be noted that this protective effect did not extend to basal cell carcinoma and that the study was underpowered to assess effect on melanoma risk [6]. Sun avoidance and clothing protection remain the mainstays of skin cancer prevention as well.

Diet. Multiple components of the diet have been studied for their effects on cancer risk. However, study of diet has proven difficult [7].

Total dietary fat appears to affect the incidence of prostate cancer but has not been consistently proven to affect rates of colon or breast cancer. Fat intake is generally evaluated with adjustments for caloric intake and weight gain in order to isolate any effects of the fats themselves. Individuals with high levels of consumption of red meat have been found to have an increased risk of colorectal cancer [7].

Some dietary practices appear to reduce cancer risk. The link between fruit and vegetable intake and decreased overall cancer risk is weak; however, pooled analyses suggest a 25% reduction in the incidence of distal (but not proximal) colon cancer in those who consumed more than 800 g of fruits and vegetables per

day. Studies focused on tomato products suggest a benefit for prostate cancer risk, possibly due to the lycopene content in these foods [7].

Consumption of calcium has been associated with a decreased incidence of any cancer in women and a decreased incidence of colon cancers in both men and women. Epidemiologic studies have found that increased fiber intake is associated with a decreased risk of colon cancers and adenomas; however, clinical trials of a high-fiber diet showed no effect on the rates of adenoma recurrence [7].

Overall, dietary recommendations from the American Cancer Society (ACS) include:

1) eating a variety of healthful foods, with 5 or more servings of vegetables and fruits per day;

2) use of whole grains in preference to processed (refined) grains and sugars;

3) limited consumption of red meats, especially processed meats and those high in fat [7].

Exercise. Estimates indicate that a sedentary lifestyle is responsible for approximately 5% of cancer deaths. Higher levels of physical activity have been associated with decreases in the risks of colon and breast cancers, and possible decreased risks of endometrial, prostate, liver, pancreatic, stomach, and lung cancers have been described as well. For colon and breast cancers, the benefit of physical activity has been demonstrated at multiple weight levels, which implies that the effect of the activity is independent of an effect of weight reduction. The mechanism of the protective effect remains uncertain but may be related to effects on immunity, hormone levels, or prostaglandins.

The frequency, duration, or intensity of exercise needed to prevent cancer has not been determined definitively. The ACS recommends that adults engage in moderate exercise for at least 30 min on 5 or more days per week. Increasing the length of exercise to 45 min or more may provide additional protection against breast and colon cancer. For children, the recommendation is to exercise for at least 60 min per day on at least 5 days per week [2].

Obesity. Epidemiologic studies have indicated that excess weight or obesity result in 14% of cancer deaths in men and 20% of cancer deaths in women. The cancers associated with obesity are similar to those associated with decreased physical activity. Excess weight has been found to account for 10-40% of colorectal, endometrial, renal, esophageal, and postmenopausal breast cancers.

Possible links have also been described for some hematologic malignancies and cancers of the prostate, liver, gallbladder, pancreas, stomach, ovary, and cervix, as well. Interventions such as bariatric surgery may reduce the risk of cancer deaths by as much as 60% [2, 7].

Alcohol use. Long-term alcohol use has been associated with approximately 4% of incident cancer cases. One alcoholic beverage per day increased overall cancer risk by 6%. The increase in cancer incidence in this group involved increased risks of cancers of the head and neck, esophagus, rectum, liver, and breast [8].

The mechanism of carcinogenesis associated with alcohol use is not fully understood at this time but may involve inflammatory, epigenetic, hormonal, or metabolic effects. Several of the metabolites of ethanol have been identified as carcinogens [8]. The ACS recommends limiting alcohol use to 2 drinks per day for men and 1 drink per day for women (due to the slower metabolism of alcohol by women). A drink is 12 ounces (oz) of beer, 5 oz of wine, or 1,5 oz of 80-proof liquor.

Hormone replacement therapy. The duration of a woman's exposure to endogenous estrogen affects breast cancer risk. Support for this hypothesis includes the increased risk of breast cancer for women with an earlier age of menarche, later age of menopause, nulliparity, and later age at first live birth, as well as higher serum estrogen concentrations. For women who take estrogen-only HRT, meta-analyses of epidemiologic studies indicate a mildly increased risk of breast cancer [9].

Combination therapy with estrogen-progestin HRT did demonstrate a significantly increased risk, with a hazard ratio of 1,2. This risk remained elevated

for several years after discontinuation of combination therapy but then declined rapidly [9].

HRT has been shown to increase breast density, which, in turn, decreases the sensitivity of mammograms. The postmenopausal women on combination progesterone/estrogen replacement had an average increase of 6% in mammographic density, whereas their counterparts taking placebo had an approximately 1% decrease over the same period [9].

Environmental and occupational exposures. Geographic patterns of cancer incidence may provide insight into cancer etiology. Possible risk factors include environmental exposures and occupational exposures from the air or water.

Workplace exposure to chemicals such as coal-tarbased products, benzene, cadmium, uranium, asbestos, or nickel can significantly increase cancer risk. For example, a significant proportion of bladder cancers may be due to chemical exposures in the aluminum, dye, paint, petroleum, rubber, and textile industries. Occupational exposures to radon and asbestos have been linked to lung cancer, and a small percentage of lung cancers are attributable to air pollution. Arsenic exposure has also been linked to increased incidence of nonmelanoma skin cancers [10].

The International Agency for Research on Cancer (IARC) has conducted extensive evaluations of potential carcinogens based on data from epidemiologic and animal studies. They define a carcinogenic agent as one capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity [10]. At this time, 108 agents are classified as group 1, or agents that are known to be carcinogenic to humans. Another 66 agents are classified as group 2A, or probable carcinogens in humans.

Infectious exposures. Approximately 17% of cancers occurring worldwide may be attributed to an infectious etiology [3]. The primary cancers with known associations with viral infections include:

- Cervical and anogenital cancers (human papillomavirus [HPV]),
- Hepatocellular carcinoma (HCC) (hepatitis B [HBV]and C [HCV]) [10],

- Kaposi sarcoma (human herpes virus [HHV]-8),
- Adult T-cell leukemia (human T-cell lymphotropic virus -1 [HTLV-I]),
- Several types of non-Hodgkin lymphoma (Epstein-Barr virus and HHV-8).

Infection with human immunodeficiency virus (HIV) also increases the risk of Kaposi sarcoma and non-Hodgkin lymphoma. In some instances, these cancers may be acquired immunodeficiency syndrome (AIDS) – defining malignancies.

Measures to prevent transmission of viral carcinogens include vaccination against carcinogenic types of HPV, use of sterile needles in the healthcare and community (eg, tattoo and drug use) settings, and screening of potential blood donors [2, 10].

For individuals who are infected with a virus that has the potential to cause cancer, several interventions are possible. Treatment of HIV infection with highly active antiretroviral therapy can prevent lymphomas associated with this virus [3]. Similarly, treatment of chronic HBV infection with interferon or nucleotide analogues to reduce the viral load also decreased the incidence of hepatocellular carcinoma [10]. Alcohol avoidance may also decrease the development of hepatoma in those with chronic hepatitis.

Bacterial infection with Helicobacter pylori is associated with risk of gastric cancer. Some data suggest that eradication of *H.pylori* infection through regimens of antibiotics and proton pump blockers may be effective as primary prevention of gastric cancer [10].

Sexual activity. Because some viral carcinogens are transmitted via bodily fluids, increased numbers of sexual partners or sexual contact with infected partners can increase the risk of these cancers. Although most women are exposed to HPV in their lifetime, infection is usually transient. When this virus cannot be cleared by the body, cervical cancer may develop. For this reason, individuals who have multiple sexual partners or who have a compromised immune system are more susceptible to HPV infection.

Means of reducing sexual transmission of carcinogenic viruses include awareness of the sexual and medical history of partners and use of barrier methods such as a condom during sexual intercourse.

Screening and Early Detection

Breast Cancer Screening can include different tests, of which clinical breast examination and mammography are commonly used.

Breast self-examination. Many experts continue to include self-examination in their recommendations due to the low cost and the benefit of making the patient an active participant in her health.

Clinical breast examination. When performed correctly by trained medical personnel in combination with mammography, clinical breast examination has greater sensitivity but a higher false-positive rate than mammography alone. In practice, nonstandardized breast examinations have a sensitivity of about 36% but detect about 5% of cancers not visible on mammograms [11]. In settings in which mammography is available, clinical breast examination may provide a slight improvement in breast cancer detection; this is a cost-effective measure in countries that do not have access to imaging resources.

Mammography. Since 1990, the mortality rate from breast cancer has been declining approximately 2% per year [2]. A study using several statistical models estimates that use of screening mammograms accounts for 28-65% of that reduction (median, 46%). A meta-analysis of randomized controlled trials showed a significant 34% reduction in breast cancer mortality at 7 years in those who had mammographic screening [11]. A subsequent review indicated that the survival benefit from mammography was greater in women older than 50 years than in those between the ages of 40 and 49 years. However, numerous other studies have demonstrated decreased mortality in women in their 40s as well [12].

Types of mammograms in use include film mammograms and digital mammograms. Images from digital mammograms are electronically captured and stored, whereas those from film mammograms are provided via traditional radiographic films. Overall, cancer detection rates are similar regardless of which

type of mammogram is used [2, 12]. The exceptions to this rule are that digital mammography is more accurate in premenopausal women and in women with dense breasts [12].

Most experts agree that screening mammography should be performed routinely in women between the ages of 50 and 69 years. However, considerable controversy exists regarding the frequency of screening in this population and regarding the optimal screening approach to women outside of this age range.

For women between the ages of 50 and 69 years, some guidelines recommend annual mammography, whereas others advocate biennial or annual examination. One observational study comparing annual and biennial screening showed no significant disadvantage from the biennial schedule in terms of detection rate or stage at time of diagnosis [13].

For women between the ages of 40 and 49, the breast cancer incidence and the sensitivity of mammograms are both lower than they are in women aged 50-69 years. The mammographic screening guidelines vary for this group of patients. Some guidelines advocate for annual mammograms in this population [13]. Other groups recommend deferring mammography until the age of 50 years in the absence of family history or other risk factors. The American College of Physicians (ACP) and the Advisory Committee on Cancer Prevention in the European Union advise discussion of screening with patients and shared decision-making [13].

Data are conflicting in this area: a significant decrease in breast cancer mortality was found on meta-analysis of those who started screening in their 40s [12] but not in a larger randomized clinical trial of annual mammography versus usual care. A cost-effectiveness study has shown that mammograms cost $21400 per year of life saved for women aged 50-69 years, whereas the cost was $105000 per year of life saved for women in their 40s [12]. Although the cost for women in their 40s was 5-fold higher, both of these values fall within the accepted range for cost effectiveness.

The most recent guideline in this area was issued by the US Preventive Services Task Force (USPSTF) in 2009, which recommended against routine mammography in women aged 40-49 years, instead advocating that physicians discuss the risks and benefits of biennial screening with women in this age group. This recommendation has been met with considerable controversy [2, 13].

Mammographic screening for women over the age of 70 years has also generated some controversy. Due to shorter life expectancy, the potential effect on mortality in this population is more difficult to assess. Two studies have demonstrated decreased breast cancer mortality in women aged 65 to 74 years, but these results did not achieve statistical significance in either study [13]. A separate study of mammographic screening in women older than age 80 years did not find an effect on rate of diagnosis, stage, or mortality. However, cost-effectiveness analysis has shown a cost per life-year gained that is within generally accepted values for continued use [13].

It has been suggested that bone mineral density (BMD) be incorporated into decision-making for breast screening for individuals in this 70-79 year age group, as those with higher bone density have an increased risk of breast cancer compared with those with low bone mineral density [13].

The false-positive rate of mammography is approximately 11% in the US. Risk factors for a false-positive result include younger age, previous breast biopsy, family history of breast cancer, current estrogen use, inconsistent screening, and lack of previous mammograms for comparison [13]. Women with a false-positive result on a mammogram will be called back for additional imaging and possible biopsy of a lesion that is ultimately found to be benign.

Overdiagnosis, or screen detection of cancers that would normally not cause clinical morbidity or affect mortality, remains an issue with mammography. Estimates of overdiagnosis range from 1 in 3 to 1 in 6 cancers detected by screening mammogram [13].

Some women express concern regarding the radiation associated with regular mammographic screening. Direct data regarding the risk associated with

this level of radiation exposure are lacking, but a study of a risk model comparing the risk of radiation and the mortality benefit of mammographic detection concluded that the net effect of mammograms was positive for women older than age 40 years. It is important to note that women with *BRCA* mutations may be more susceptible to the effects of radiation to the breast. Studies of *BRCA* carriers showed that those with exposure to chest x-rays were 54% more likely to develop breast cancer; this risk increased with multiple x-rays or x-rays done at an early age. In contrast, a study of mammograms in another *BRCA* population did not find an increased risk of breast cancer in a multivariate model [13].

Breast ultrasonography. In the US, breast ultrasonography is not usually performed as a screening study. Investigations into the combination of ultrasonography and mammography for screening have shown increased sensitivity but decreased specificity with the addition of ultrasonography [13]. Although ultrasonography remains a tool for diagnosis, it is not a tool for screening of the breast.

Breast magnetic resonance imaging (MRI) is not used for routine screening in the general population, and no studies of the effect of screening breast MRI on breast cancer mortality have been published to date. In women at high risk of breast cancer, a comparison of breast MRI and mammography showed that MRI was significantly more sensitive but less specific than mammography. Women who undergo screening with breast MRI must be made aware of the increased risk of a false-positive result that requires additional studies or a biopsy [13].

Guidelines published by the American Cancer Society recommend annual breast MRI (usually in addition to annual mammography) for the following patients:

- Women who are carriers of mutations in the *BRCA* genes or other germline mutation carriers with a known markedly increased risk of breast cancer.
- First-degree relatives of mutation carriers who have not been tested themselves.

- Women who have a history of radiation to the breast between the ages of 10 and 30 years.
- Women with a lifetime risk of breast cancer estimated at 20% or greater according to family history-based risk assessment models (eg, BRCAPro, Myriad, Tyrer-Cusick).

Additional data are required before making a recommendation for or against screening with breast MRI in those who have a personal history of breast cancer, those with precancerous conditions such as lobular carcinoma in situ (LCIS) or atypical hyperplasia, those with dense breasts, or those who have a 15-20% lifetime risk of breast cancer. MRls are not recommended for those with a lifetime breast cancer risk of less than 15%.

The National Institute for Health and Clinical Excellence (NICE) also issued guidelines for screening with breast MRI. These guidelines suggest annual MRI and mammography be done for the following patients [2, 13]:

- Women with *BRCA* mutations who are age 30 years and older.
- Tumor-suppressor protein p53 (*TP53*) mutation carriers aged 20 years and older.
- Women in their 30s with a 10-year risk >8%.
- Women in their 40s with a 10-year risk >20%.
- Women in their 40s with dense breasts and a 10-year risk >12%.

Cervical Cancer Screening. The Papanicolaou (Pap) smear is the standard screening test for cervical cancer. HPV is the etiologic agent for most cervical cancers.

Pap smears consists of sampling and examination of the cells at the transformation zone at the junction between the endocervix and ectocervix, which is the site of cervical dysplasia and cancers.

The efficacy of the Pap smear has never been evaluated in a randomized clinical trial, although an observational study in Canada showed a decrease in cervical and uterine cancer mortality rates in areas with high screening rates by Pap smear; areas with low rates showed an increase in mortality from these cancers. As

the use of Pap smears to screen for cervical cancer became implemented internationally, many other countries reported corresponding declines in cervical cancer incidence and mortality. A case-control study found that lack of a Pap smear within the 5 years before a cervical cancer diagnosis conveyed a 3-fold increase in risk of invasive cancer [14].

Two methods of Pap smears are in current use:

- the conventional smear;
- liquid-based cytology.

The performances of these tests are similar for identifying high-grade squamous lesions with the potential to develop into cancer. Low-grade lesions and atypical squamous or glandular cells are better detected by the liquid-based technique [14]. The specimen adequacy is better with the liquid-based cytology, but it is not clear that this result represents a clinically significant benefit. An additional benefit of the liquid-based testing is that the same specimen may be used for the Pap smear and for HPV testing. Cost and availability of liquid-based testing measures are other factors that figure into the decision of which method to use.

Approximately 6-7% of Pap smears per year are read as abnormal. Sensitivity and specificity of this test vary substantially: estimates of the sensitivity range as 30-87%, whereas specificity is reported as 86-100% [14].

All guidelines for cervical cancer screening recommend starting Pap smears at age 21 years or 3 years after the onset of sexual activity. However, the guidelines vary in their recommendations for the age at which screening should be stopped: the USPSTF advises stopping at age 65 years, the American Cancer Society recommends ending screening at age 70 years if previous Pap smears have been normal, and the American College of Obstetrics and Gynecologists indicates that the age to stop screening should be determined on an individual basis.

Frequency of screening also varies among the guidelines. Data have indicated that the incidence of cervical cancer detection was only slightly lower with a screening interval of every 3 years, as compared with every year [15]. The

USPSTF advocates for screening at least every 3 years, whereas the other 2 groups suggest annual Pap smears for women younger than 30 years and screening every 2-3 years for women older than 30 years with 3 consecutive normal tests [15, 16].

Women who have undergone total hysterectomy (with removal of the cervix) for benign causes do not need cervical screening; however, those who have a history of cervical or uterine cancer should continue to have Pap smears on an annual basis. Individuals with a history of immunosuppression or diethylstilbestrol (DES) exposure in utero may also require more frequent screening.

Human papillomavirus testing. Two types of tests have been developed to identify high-risk types of HPV, the etiologic agent for most cervical cancers:

1 - identifies whether any of 14 high-risk HPV types are present. Examples of this type of test include the Hybrid Capture 2 and the Cervista HPV HR test;

2 - detects HPV types 16 and 18 (as exemplified by the Cervista HPV 16/18 test), which are responsible for the majority of cervical cancers and high-grade cervical lesions.

HPV testing has been studied alone and in conjunction with Pap smears. This test does have a greater sensitivity than cervical cytology alone; however, its specificity is lower [15, 16].

Primary HPV testing is not recommended for women younger than 30 years, as the rate of false-positives is higher in this population. Those older than 30 years who undergo primary HPV testing require a Pap smear to follow up a positive HPV result. Consensus guidelines recommend that women with negative Pap smear and negative HPV testing do not require screening for at least 3 years [16]. Those with a positive HPV test and a negative Pap smear need to repeat both tests in 1 year; if the tests are negative at that time, the women can return to screening every 3 years.

Screening recommendations by the American Cancer Society and the American College of Obstetrics and Gynecologists suggest that the screening interval may be increased to every 3 years if HPV testing is done in addition to

cervical cytology. At this time, the USPSTF has made no recommendations regarding use of HPV testing [15, 16].

Colon Cancer Screening. Colon cancer screening can be performed using a variety of methods; there are a total of 7 testing options recommended [17]. The screening modalities for colon cancer can be classified into 2 general categories: stool-based tests and endoscopic or radiologic examinations.

Stool-based tests have the ability to detect early cancers and may detect advanced adenomas. The first of these tests, the guaiac-based fecal occult blood test (gFOBT), has been shown in clinical trials to reduce colon cancer mortality by up to 33% when done on an annual basis [17]. Advantages of this test include its low cost and noninvasive method. The specificity of the gFOBT is low, giving the potential for many false-positive results that require additional testing, such as colonoscopy. Patients should avoid nonsteroidal anti-inflammatory drugs (NSAIDs), red meat, and high doses of vitamin C (>250 mg) for 48 hours before and during the testing period, and samples should be collected from 3 consecutive stools.

More recently, immunochemical-based FOBTs (also known as fecal immunochemical tests) and the stool DNA panel have also become available. The cost of the immunochemical test is greater than that of the guaiac-based test, but the specificity may be higher. Stool DNA panels are also expensive and require a greater quantity of stool to perform the test. The suggested screening interval is every 5 years.

Endoscopic and radiographic tests that image the colon and rectum have the potential to detect not only cancers but adenomatous polyps that may develop into cancers. Endoscopic tests such as flexible sigmoidoscopy and colonoscopy have been in use as screening tools for many years. Although clinical trials have not addressed the effect of these endoscopic modalities on colorectal cancer mortality in the general population, observational studies have shown that flexible sigmoidoscopy may significantly reduce deaths from colorectal cancers that occur in the area visualized by this scope [17].

The major limitation of flexible sigmoidoscopy is that it visualizes only the distal 60 cm of the colon. Abnormal results require examination of the entire colon by colonoscopy. The recommended screening interval for flexible sigmoidoscopy is every 5 years. Colonoscopy, however, requires significant bowel preparation and carries the risk of complications such as bleeding or bowel perforation. If there is no evidence of polyps, colonoscopy is repeated every 10 years for screening.

Double-contrast barium enema has also been included as a colon cancer screening option. Although this test is a safe means to visualize the entire bowel, its sensitivity is poor and positive results require additional evaluation with colonoscopy. The most recent USPSTF recommendations do not consider barium enema for colon cancer screening. In the absence of an abnormal result, barium enema is recommended to be performed every 5 years.

Computed tomography (CT) colonography, formerly referred to as «virtual colonoscopy», has been a more recent development. Similar to optical colonoscopy, this modality visualizes the entire bowel and requires a bowel preparation; however, CT colonography does not pose the risks of complications associated with optical colonoscopy. Positive results require colonoscopy to obtain a biopsy. There is also a risk associated with the cumulative radiation exposure for this test, which could become significant if it is performed regularly for screening. CT colonography should be performed every 5 years.

Guidelines. Several different groups have produced guidelines for colorectal cancer screening. All of the tests listed above are endorsed by the Multi-Society Task Force. This group encourages physicians and patients to discuss the screening options in terms of early detection (stool-based tests) or prevention (radiographic or endoscopic tests), and then to select a test within the chosen category. Screening is recommended to start at age 50 years in individuals who are at average risk of colon cancer and to continue until the patient's life expectancy is less than 10 years.

The recommendations of the American College of Gastroenterology differ in several respects [17]: prefers colonoscopy and fecal immunochemical testing as

well as recommends starting screening in black individuals at age 45 years rather than 50 years. The USPSTF guidelines prefer 3 screening strategies: FOBT every year, colonoscopy every 10 years, or the combination of flexible sigmoidoscopy every 5 years and FOBT every 3 years [17]. The age range put forward for screening in these guidelines is age 50-75 years.

Individuals who are at increased risk of colon cancer due to a personal history of polyps, inflammatory bowel disease (IBD), or previous colorectal cancer or a family history of colorectal cancer should have screening by colonoscopy. The age at which screening is initiated may also be earlier for these individuals, based on the youngest age at which a family member was diagnosed with colorectal cancer or the time of onset of symptoms from inflammatory bowel disease. The examinations should be performed more frequently in these individuals as well, with annual colonoscopy recommended for those at genetic risk and colonoscopy every 1-2 years for those with inflammatory bowel disease. For individuals with a first-degree relative with colorectal cancer but no evidence of a genetic syndrome, screening should start at age 40 years and be repeated every 5 years.

Individuals with a personal history of adenoma should have repeat colonoscopy 3-5 years after the polyp has been removed, with the interval determined on the basis of the histology and number of polyps identified. For very large polyps that may not have been completely resected, short-term repeat colonoscopy several months later may be appropriate. Subsequent intervals for colonoscopy should be 5-10 years in individuals with polyps. For those with a personal history of colon cancer, colonoscopy should be repeated 1 year after cancer diagnosis, then in 1-3 years (based on findings at the 1-year colonoscopy). If no further pathology is identified, colonoscopy should continue at intervals of no more than 5 years for subsequent screening [17].

Endometrial Cancer Screening is not recommended for the general population. Cervical cytology is not sensitive enough to be a reliable screening test for endometrial cancer, although it is effective in detecting pathology of the squamous cells of the cervix [17], and endometrial biopsy is an invasive procedure

that often does not result in an adequate specimen. The benefit from presymptomatic diagnosis of endometrial cancer is unclear, as the majority of cancers present as dysfunctional uterine bleeding (DUB) and are diagnosed while still confined to the uterus (stage I).

Women who are at increased hereditary risk of endometrial cancer from Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]) or from Cowden syndrome are recommended to undergo annual endometrial biopsy starting at age 35 years. Transvaginal ultrasonography has also been recommended for this group, although some evidence suggests that this procedure is not effective in early detection of cancers [17].

Lung Cancer Screening. Currently, screening for lung cancer in asymptomatic individuals is not recommended. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial is investigating the use of chest x-rays as a screening tool for smokers and nonsmokers. Another study is evaluating chest x-rays and CT scans as screening strategies for current and former smokers.

Ovarian Cancer Screening. Detection of early stage ovarian cancer has proved difficult: three quarters of ovarian cancers show spread beyond the ovary at the time of diagnosis. Although current guidelines do not recommend screening for ovarian cancer for women in the general population [17], screening tests such as the serum biomarker CA125 and transvaginal ultrasonography are frequently used in combination to monitor women who are at increased risk of ovarian cancer due to genetic mutations in *BRCA* or mismatch repair genes.

Serum CA125 levels have fair sensitivity for advanced ovarian cancer but poor specificity [17]. A small proportion of healthy women have elevated CA125 levels, and these levels can also be affected by age, smoking status, the menstrual cycle, endometriosis, cirrhosis, fibroids, pelvic inflammatory disease (PID), pleural or peritoneal fluid, or other types of cancers [17]. A change in CA125 level over time may be a more effective means of assessing for ovarian neoplasms.

A panel of serum proteins, including CA125, was marketed in the US as a screening test for ovarian cancer under the brand name OvaSure. However, this

test was designed for a population that had a much higher prevalence of ovarian cancer than that of the general population in the US [2, 17]. Concerns about the validity of this test in the general population led to its removal from the market.

The main imaging modality that has been evaluated for ovarian cancer screening is transvaginal ultrasonography. Although its specificity is good, the sensitivity of screening with this modality varies significantly based on the experience of the operator. Clinical trials to determine whether transvaginal ultrasonography can diagnose early stages of ovarian cancer have had conflicting results: all cancers detected in high-risk women were stage III. However, other studies conducted in lower-risk populations did have a significant proportion of early disease among the cancers detected [17].

The effects of screening on the early detection and mortality rates of ovarian cancer in women at average risk are being assessed in 3 large, randomized, controlled trials [17, 18]. Each of these studies involves multimodal screening with both transvaginal ultrasonography and serum CA125 testing, with transvaginal ultrasonography or usual care as control groups.

Because of the higher prevalence of ovarian cancer in women at high risk, the predictive value of screening is higher in this population; therefore, some expert groups do endorse screening of high-risk women. However, the screening interval is not specified by all groups: women who are at high risk of ovarian cancer due to a strong family history or a deleterious mutation should have both transvaginal ultrasonography and CA125 testing every 6 months, starting at age 35 years or 5-10 years before the earliest cancer in the family [17, 18].

Prostate Cancer Screening. The mainstays of prostate cancer screening are measurement of prostate-specific antigen (PSA) and digital rectal examination (DRE). PSA testing originated as a tumor marker to assess recurrence or disease progression for men with a history of prostate cancer; however, it was adopted for screening in the general population before this use was evaluated in randomized trials. Later studies had mixed results: it was found a survival benefit associated with PSA screening, whereas the PLCO study did not find a benefit associated

with screening by PSA and digital rectal examination. Measurement of PSA can be affected by factors other than prostate cancer, including benign prostatic hypertrophy (BPH), ejaculation, bacterial prostatitis, urinary retention, and use of medications such as 5-alpha reductase inhibitors [17, 18].

Prostate biopsy has also been shown to cause significant elevations in PSA sustained for up to 1 month, whereas digital rectal examination is not felt to have a substantive effect on PSA measurements. Overall, when abnormal PSA values are defined as those over 4,0 ng/mL, the sensitivity of the PSA test is 70-80% and the specificity is 60-70%. An exception is the Prostate Cancer Prevention Trial, which showed a sensitivity of 21% for PSA at this level [19].

Several approaches have been taken to try to improve the utility of PSA measurement, including use of PSA velocity to assess change over time, PSA density to adjust values according to prostate volume as measured by ultrasonography or MRI, the ratio of free to total PSA, and complexed PSA, as well as individualized reference ranges based on age or race. However, these modified values have not replaced standard PSA testing in most practices.

Despite the long-standing use of digital examination of the prostate through the rectum (ie, digital rectal examination), there have been no controlled studies that demonstrated an effect of this test on prostate cancer mortality or incidence. Assessment of the prostate by this technique often results in inconsistent results, even among specialists. The sensitivity has been estimated at 59% and the specificity at 94%. Clinically, the overall sensitivity is improved when digital rectal examination and PSA are used in combination, although PSA appears to outperform digital rectal examination in some aspects [20].

Guidelines regarding screening for prostate cancer with PSA testing and digital rectal examination vary considerably. Several groups recommend discussion of the risks and benefits of screening with the patient and individualizing decisions [20]. The American Cancer Society and American Urological Association recommend consideration of starting screening at age 50 years for most men and at age 45 years for men who are at increased risk of

prostate cancer due to family history or ethnic background. Their regimen consists of annual PSA testing and digital rectal examination for all men who have a life expectancy of at least 10 years and who desire screening.

Numerous other groups find the evidence insufficient to support screening at this time. The USPSTF feels that the potential harms associated with screening individuals older than 75 years exceed the potential benefits, and the Canadian Task Force recommends against use of PSA for screening in any age group.

Vaccines and Medical Prevention

Breast Cancer. At present, 2 medications are available for the primary prevention of breast cancer: tamoxifen and raloxifene. These drugs are selective estrogen receptor modulators (SERMs) that have both estrogen agonist and antagonist effects.

Tamoxifen. The Breast Cancer Prevention Trial (BCPT) found that, compared with patients receiving placebo, tamoxifen users had a 50% reduction in the incidence of invasive and noninvasive estrogen receptor-positive breast cancers. The investigators evaluated the use of tamoxifen for the prevention of breast cancer in women at increased risk based on age older than 60 years, personal history of lobular carcinoma in situ, or a 5-year Gail score of more than 1,66%. On long-term follow-up, the protective effect of tamoxifen persisted, with approximately 43% reduction in invasive cancer risk [20]. However, tamoxifen was also shown to produce an approximately 2-fold increased risk of endometrial cancer and thromboembolic events, including stroke.

A second study found a significant reduction in the incidence of breast cancer in tamoxifen users, but the all-cause mortality rate was higher in the tamoxifen intervention group [20]. A meta-analysis concluded that use of tamoxifen reduced breast cancer risk by 38% and doubled the risk of endometrial cancer and thromboembolic events, but it did not affect overall mortality [21].

The USPSTF does not recommend use of tamoxifen for chemoprevention of breast cancer in women of average risk. For those who have an increased risk due to family history, *BRCA* or other mutation carrier status, or conditions such as

lobular carcinoma in situ, the benefits of treatment must be balanced against the risks of side effects on an individual basis [21].

Raloxifene. In the study of tamoxifen and raloxifene (STAR) trial, in which raloxifene was compared with tamoxifen for prevention of breast cancer in postmenopausal women, the incidence rates for invasive breast cancer were similar with both drugs, but the risks of thromboembolic adverse effects and endometrial cancer were significantly lower with raloxifene. Although the rate of noninvasive breast cancer was higher in the raloxifene group than in the tamoxifen group, this difference did not achieve statistical significance. The profile of other side effects also differed between the 2 groups: tamoxifen was associated with higher rates of gynecologic problems, vasomotor symptoms, and bladder symptoms, whereas sexual dysfunction, musculoskeletal issues, and weight gain were more frequent with raloxifene [21].

The US Food and Drug Administration (FDA) approved raloxifene for use for breast cancer chemoprevention in postmenopausal women. This drug has not been studied in premenopausal women and is not approved for use in this population. To date, there are no reports on the use of raloxifene in *BRCA* mutation carriers.

Cervical Cancer. Two vaccines have been developed against HPV, the etiologic agent of most cases of cervical cancer: Gardasil (Merck & Co, Inc. Whitehouse Station, NJ) and Cervarix (GlaxoSmithKline Biologicals, Rixensart, Belgium). Gardasil is a quadrivalent vaccine that acts against HPV genotypes 6, 11, 16 and 18. The HPV-16 and HPV-18 genotypes cause almost two thirds of all cervical cancers and cervical intraepithelial neoplasia (CIN) 2 and 3, whereas the the HPV-6 and HPV-11 genotypes are implicated in genital warts. Cervarix is a bivalent vaccine that also targets HPV-16 and HPV-18.

Both vaccines are given in 3 doses over a 6-month period. Each of the vaccines has been shown to be very effective in the prevention of CIN 2/3 or cervical cancers in subjects who had not been previously exposed to HPV. However, neither vaccine showed strong efficacy in preventing premalignant or

malignant cervical disease in subjects who were not HPV-naive; nor did the vaccines show efficacy in the treatment of existing HPV infections [21].

Because cervical cancers can be caused by HPV genotypes other than those contained in the vaccines, cervical screening with Pap smears should be continued after vaccination. However, the duration of protection against HPV after vaccination remains unknown.

The most frequent side effect associated with vaccination was a mild reaction at the injection site. Postlicensure surveillance reports for Gardasil also indicated increased risk of postvaccination syncope and thromboembolic events; nearly all thromboembolic events occurred in those with a known risk factor, such as oral contraceptive use or family history of thromboembolic disease [21]. Postlicensure data are not available for Cervarix.

Several groups have made recommendations regarding the appropriate use of HPV vaccinations. The vaccination should be offered to girls before their becoming sexually active (ACIP: age 11-12 y; ACOG: age 13-15 y) [22]. Both groups advocate «catch-up» vaccination for females between the ages of 13 and 26 years if they have not had previous vaccination, and they indicate that vaccination may occur as early as age 9 years. HPV testing is not recommended before vaccination.

The WHO also recommends vaccinations for girls between the ages of 9 and 13 years; however, the American Cancer Society recommends girls between the ages of 11 and 18 years be offered vaccination [22]. These guidelines did not support catch-up vaccination, indicating that additional evidence of benefit was needed for those older than 18 years.

Male vaccination for HPV is not recommended. However, vaccination of males remains a consideration, both to prevent reinfection of their female sexual partners and to prevent genital warts and anal or penile cancers. Data for this indication are under review at the FDA.

HPV vaccination has not been studied in immunosuppressed or immunocompromised individuals; therefore, at this time, vaccination is not specifically recommended for those in this group.

Prostate Cancer. 5-alpha reductase inhibitors have been shown to have protective effects against prostate cancer in clinical trials. Meta-analysis of 5-alpha reductase inhibitor studies indicates that these agents decrease the risk of prostate cancer by approximately 25% [22].

Finasteride. The Prostate Cancer Prevention Trial (PCPT), which compared finasteride to placebo in nearly 19000 men who were at increased risk of prostate cancer due to age, ethnic background, or family history of prostate cancer, was closed early due to a 25% decrease in numbers of prostate cancer in the finasteride group relative to the control group. However, the finasteride group was noted to have more aggressive cancers (Gleason score >6) [22].

Several possible explanations for this result have been presented, including diagnostic bias due to decreased prostate volume in the participants taking finasteride and detection bias due to the effects of finasteride on PSA testing. Finasteride decreases PSA levels by 50% on average [22].

Side effects included gynecomastia and sexual dysfunction, which was mild and decreased over time. It remains unclear whether finasteride decreases mortality from prostate cancer.

Dutasteride. Preliminary results from the REDUCE (REduction by DUtasteride of prostate Cancer Events) trial, which investigated dutasteride, another 5-alpha reductase inhibitor, as a chemopreventive agent for men at increased risk of prostate cancer showed a 23% decrease in prostate cancer incidence in the dutasteride arm, which achieved statistical significance [22]. Unlike the PCPT trial, the incidence of high-grade cancers was not increased in the REDUCE study. Final results on this study are pending.

Guidelines from the American Society of Clinical Oncology and the American Urologic Association recommend that men discuss the risks and benefits of chemoprevention with these medications with their physicians [22, 23].

Surgical Prevention

For individuals at very high risk of cancer, such as those with hereditary genetic predisposition, surgical intervention provides another means of risk reduction. Main examples of surgical management of cancer risk include prophylactic mastectomy in *BRCA* mutation carriers, prophylactic salpingo-oophorectomy in *BRCA* carriers and mismatch repair gene mutation carriers, and prophylactic colectomy in individuals with familial adenomatous polyposis.

Prophylactic mastectomy has been a mainstay of management of *BRCA* mutation carriers because of their markedly increased risk of breast cancer. The breast cancer risk reduction associated with bilateral prophylactic mastectomy is approximately 90%. Simple or skin-sparing mastectomy techniques are preferred over subcutaneous mastectomy, because the latter technique tends to leave more residual breast tissue with the potential to develop cancer [21].

Despite the considerable risk reduction associated with this procedure, utilization of prophylactic mastectomy remains far less than that of prophylactic salpingo-oophorectomy. Possible reasons for the discrepancy between the rates of these prophylactic surgeries include lack of data proving survival benefit, concerns about appearance and sexuality following mastectomy, availability of medications that reduce breast cancer risk, and the options of screening modalities that can detect breast cancer at a premalignant or early stage.

Prophylactic salpingo-oophorectomy has primarily been studied in women with *BRCA1* or *BRCA2* germline mutations, although it is also appropriate for women with Lynch syndrome (hereditary nonpolyposis colorectal cancer) and some other hereditary syndromes. This procedure provides premenopausal *BRCA* mutation carriers with protection from both ovarian cancer (90-95% risk reduction) and breast cancer (50% risk reduction); for postmenopausal carriers, it provides protection from ovarian cancer only. Even after oophorectomy a small risk of primary peritoneal cancer remains [23].

Prophylactic gynecologic surgery has been shown to improve overall and cancer-related survival in this population. Risk-reducing surgery dramatically decreases the incidence of cancer in the Lynch syndrome population as well [23].

For *BRCA* mutation carriers, experts recommend that bilateral salingo-oophorectomy take place between the ages of 35 and 40 years or after childbearing are complete. The fallopian tubes should be removed as well, due to the increased incidence of fallopian tube carcinoma in this population. Careful pathology review of both the ovaries and fallopian tubes is vital to detect clinically occult cancers, which is reported in approximately 4-8% of women undergoing this procedure [23].

Prophylactic hysterectomy at the time of oophorectomy remains a point of some debate. For women with Lynch syndrome, the risk of endometrial cancer is also increased, and it is appropriate to remove the uterus at the time of oophorectomy. Although *BRCA* mutations are not generally felt to increase the risk of endometrial cancer, some data suggest that the incidence of these cancers is higher than would be expected in this population [23]. These results may be due to use of tamoxifen for chemoprevention of breast cancer. Removal of the uterus could allow for more complete removal of the fallopian tubes and as well as use of unopposed estrogen for hormone replacement therapy.

Another issue of debate is the use of HRT after prophylactic oophorectomy, which remains controversial in this population due to the risks of breast cancer. At least one report has found that short-term use of HRT to treat menopausal symptoms after oophorectomy in *BRCA* carriers did not increase the incidence of cancers. However, long-term follow-up data are lacking, so careful counseling regarding the risks and benefits of hormone replacement therapy is appropriate.

Colectomy. Individuals with the hereditary syndrome familial adenomatous polyposis are often afflicted with hundreds to thousands of colorectal polyps and have a virtual certainty of developing colorectal cancer in their lifetime if their disease is unchecked. A standard risk-reducing measure in this population is prophylactic colectomy, which is generally undertaken at the appearance of

adenomas in known mutation carriers. Depending on the phenotype of the individual and other affected members of the family, surgical options include total proctocolectomy with ileal pouch and anastomosis, total abdominal colectomy with ileorectal anastomosis, or total proctocolectomy with ileostomy. For individuals who have an intact rectum after surgery, regular lower endoscopic surveillance is still recommended; surveillance of the ileal pouch should occur every 2 years in individuals who have undergone this surgical option [23].

Although the burden of cancer is daunting, primary and secondary prevention of this disease is possible in many instances. Recent trends for decreased cancer incidence and mortality in the US are largely due to improvements in risk reduction measures and early detection of cancer through screening.

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TASKS FOR FINAL CONTROL

1. The following risk factors are assessed as modifiable:

A. Age, smoking, atherogenic diet, alcohol intake, physical activity, dyslipidemias, hypertension, obesity, diabetes, metabolic syndrome

B. Smoking, sex, atherogenic diet, alcohol intake, physical activity, dyslipidemias, hypertension, obesity, diabetes, metabolic syndrome

C. Smoking, atherogenic diet, alcohol intake, physical activity, dyslipidemias, hypertension, obesity, diabetes, metabolic syndrome

D. Smoking, family history,atherogenic diet, alcohol intake, physical activity, dyslipidemias, hypertension, obesity, diabetes, metabolic syndrome

E. Smoking, sex, genetic,atherogenic diet, alcohol intake, physical activity, dyslipidemias, hypertension, obesity, diabetes, metabolic syndrome

2. The following risk factors are assessed as emerging:

A. C-reactive protein, fibrinogen, coronary artery calcification, homocysteine, lipoprotein(a), and small, dense LDL, metabolic syndrome

B. C-reactive protein, fibrinogen, coronary artery calcification, homocysteine, lipoprotein(a), and small, dense LDL

C. C-reactive protein, fibrinogen, coronary artery calcification, homocysteine, lipoprotein(a), and small, dense LDL, alcohol intake

D. C-reactive protein, fibrinogen, coronary artery calcification, homocysteine, lipoprotein(a), and small, dense LDL, high glucose level

E. C-reactive protein, fibrinogen, coronary artery calcification, homocysteine

3. Before the management of elevated blood cholesterol is initiated, the following potential secondary causes of high LDL should be considered:

A. Hypothyroidism, nephrotic syndrome, and primary biliary cirrhosis

B. Hypothyroidism, primary biliary cirrhosis, and anorexia nervosa

C. Hypothyroidism, nephrotic syndrome, primary biliary cirrhosis, and anorexia nervosa

D. Hypothyroidism, nephrotic syndrome, cirrhosis, and excessive physical exercise

E. Hyperthyroidism, nephrotic syndrome, and anorexia nervosa

4. Before the management of elevated blood cholesterol is initiated, the following potential secondary causes of hypertriglyceridemia should be considered:

A. Diabetes mellitus, chronic kidney disease, alcoholism, pregnancy, hypothyroidism, cirrhosis

B. Diabetes mellitus, chronic kidney disease, alcoholism, pregnancy, hypothyroidism

C. Diabetes mellitus, cirrhosis, alcoholism, pregnancy, hypothyroidism

D. Diabetes mellitus, chronic kidney disease, alcoholism, pregnancy, hyperthyroidism

E. Diabetes mellitus, chronic kidney and liver disease, alcoholism

5. Before the management of elevated blood cholesterol is initiated, the following potential secondary causes of low HDL should be considered:

A. Diabetes mellitus, metabolic syndrome, obesity

B. Diabetes mellitus, cigarette smoking, obesity

C. Diabetes mellitus, cigarette smoking, alcoholism

D. Diabetes mellitus, obesity

E. Diabetes mellitus, chronic kidney and liver disease

6. Dietary guidelines for prevention of cardiovascular disease recommend specific quantities of macronutrients, such as:

A. <200 mg of cholesterol per day and <7% of calories as saturated fat

B. <300 mg of cholesterol per day and <7% of calories as saturated fat

C. <150 mg of cholesterol per day and <7% of calories as saturated fat

D. <200 mg of cholesterol per day and <9% of calories as saturated fat

E. <200 mg of cholesterol per day and <6% of calories as saturated fat

7. Moderate alcohol consumption (1-2 drinks per d) is associated with a reduced overall and CHD-related mortality compared with both abstinence and heavy drinking. The effects of alcohol are attributed to:

A. raises HDL (by stimulating the hepatic production of apo A-I and A-II), stimulates fibrinolysis, reduces fibrinogen levels, reduces inflammation

B. raises HDL (by stimulating the hepatic production of apo A-I and A-II), stimulates fibrinolysis, reduces fibrinogen levels, reduces inflammation, and inhibits platelet activation

C. decrease LDL, stimulates fibrinolysis, reduces fibrinogen levels, reduces inflammation, inhibits platelet activation

D. raises HDL (by stimulating the hepatic production of apo A-I and A-II), reduces fibrinogen levels, reduces inflammation, inhibits platelet activation

E. raises HDL (by stimulating the hepatic production of apo A-I and A-II), stimulates fibrinolysis, inhibits platelet activation

8. For individuals with high-normal blood pressure (systolic 130-139 mm Hg and/or diastolic 85-89 mm Hg), the following is noted:

A. These persons have an increased risk of cardiovascular events over time compared with those who have optimal blood pressure

B. Antihypertensive drug therapy should be considered among such patients if diabetes or end-organ damage is present

C. Treatment, particularly with an angiotensin-converting enzyme (ACE) inhibitor, is also warranted in patients with renal insufficiency, diabetes mellitus, or heart failure to slow the progression of the underlying disease

D. Treatment, particularly with an angiotensin-converting enzyme (ACE) inhibitor or, if not tolerated, an angiotensin-II receptor blocker

E. All of mentioned above

9. General Nutritional Recommendations for prevention of cardiovascular disease recommend, except:

A. Eat a variety of fruits; vegetables; legumes; nuts; soy products; low-fat dairy products; and whole grain breads, cereals, and pastas; baked or broiled fish at least twice per week

B. Choose oils and margarines low in saturated fat and high in omega-3 fat, such as canola, soybean, walnut, and flaxseed oils, including those fortified with stanols and sterols

C. Avoid fatty fish

D. Limit alcohol consumption to no more than 2 drinks per day for a man or 1 drink per day for a woman

E. Eat less than 6 g of salt or <2400 mg/d of sodium

10. For prevention of cardiovascular disease the goal BP for patient with diabetes or chronic kidney disease is:

A. BP <120/80 mm Hg or <110/70 mm Hg

B. BP <135/90 mm Hg or <120/80 mm Hg

C. BP <160/90 mm Hg or <140/80 mm Hg

D. BP <140/90 mm Hg or <130/80 mm Hg

E. BP <130/90 mm Hg or <120/80 mm Hg

11. Which alcohol consumption has been significantly associated with a lower incidence of cardiovascular and all-cause mortality in patients with cardiovascular disease?

A. 15-40 g/d

B. 20-30 g/d

C. 25-35g/d

D. 5-25 g/d

E. 10-15 g/d

12.Within 24 hours of hospitalization for all hospitalized patients with an acute cardiovascular or coronary event it is recommended:

A. to assess fasting lipid profile in all patients, initiate lipid-lowering medication before discharge. If baseline LDL cholesterol level is 70 mg/dL, initiate LDL-lowering drug therapy

B. to assess fasting lipid profile in all patients, initiate lipid-lowering medication after discharge.

C. to assess fasting lipid profile in all patients, initiate lipid-lowering medication before discharge.If baseline LDL cholesterol level is 100 mg/dL, initiate LDL-lowering drug therapy

D. to assess fasting lipid profile in all patients before discharge

E. to assess fasting lipid profile in all patients, initiate lipid-lowering medication after discharge.If baseline LDL cholesterol level is 70 mg/dL, initiate LDL-lowering drug therapy

13. The initial goal of weight loss therapy to reduce body weight should be approximately

A. 5% from the baseline

B. 10% from the baseline

C. 20% from the baseline

D. 30% from the baseline

E. if waist circumference is 35 inches in women and 40 inches in men

14. In post-MI patients when clinically indicated (eg, atrial fibrillation, left ventricular thrombosis) the following medications are recommended as antiplatelet agents and anticoagulants:

A. Manage warfarin to international normalized ratio of 1,0-3,0 for paroxysmal or chronic atrial fibrillation or flutter

B.Use of clopidogrel 75 mg/day combination with aspirin for up to 12 month

C. Use of clopidogrel 75 mg/d

D. Use of warfarin in conjunction with aspirin and/or clopidogrel

E. Use of higher-dose aspirin at 162-325 mg/d

15. What components are involved in the pathogenesis of COPD?

A. **chronic bronchitis, emphysema, asthma, airflow obstruction that is not fully reversible**

B. chronic bronchitis, emphysema, asthma, airflow obstruction that is not fully reversible, high blood pressure

C. chronic bronchitis, emphysema, asthma

D. chronic bronchitis, emphysema

E. chronic bronchitis or asthma

16. What is the definition of chronic bronchitis?

A. the presence of a chronic productive cough for 5 months during the past year

B. the abnormal, permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis.

C. permanent enlargement of the air spaces distal to the terminal bronchioles

D. **the presence of a chronic productive cough for 3 months during each of 2 consecutive years (other causes of cough being excluded)**

E. the presence of a chronic productive cough for more thean 3 months

17. What is the definition of emphysema?

A. permanent enlargement of the air spaces distal to the terminal bronchioles

B. **the abnormal, permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis.**

C. the presence of a chronic productive cough for 5 months during the past year

D. the presence of a chronic productive cough for more thean 3 months

E. the presence of a chronic productive cough for 3 months during each of 2 consecutive years (other causes of cough being excluded)

18. According to the GOLD definition, COPD is:

A. a disease process that is irreversible and the therapy has little to offer

B. **a disease state characterized by airflow limitation that is not fully reversible, is usually progressive, and is associated with an abnormal inflammatory response of the lungs to inhaled noxious particles or gases**

C. the disease, that is not treatable and preventable

D. a disease state characterized by airflow limitation that is fully reversible, is usually non -progressive, and is associated with an abnormal inflammatory response of the lungs to inhaled noxious particles or gases

E. a disease state characterized by airflow limitation that is fully reversible

19. The main etiological factors of COPD are the following

A. age, gender, marital status

B. **cigarette smoking, Environmental factors, Airway hyperresponsiveness, Alpha-1-antitrypsin deficiency**

C. Diabetes mellitus, cirrhosis, alcoholism, pregnancy, hypothyroidism

D.cigarette smoking, cirrhosis, alcoholism, Diabetes mellitus

E. Age, smoking, atherogenic diet, alcohol intake, physical activity, dyslipidemias, hypertension, obesity, diabetes, metabolic syndrome

20. The exact prevalence of COPD worldwide is largely unknown, but estimates have varied

A. from 16,7-22,2%.

B. from 3,7-8,6%.

C. from 1-3%.

D. from 80-90%.

E. **from 7-19%.**

21. The multidimensional BODE index, that was developed to assess an individual's risk of death or hospitalization, includes:

A. body mass index, obstruction [FEV_1], dyspnea

B. smoking, pulmonary hypertension, obstruction [FEV1**],** and declining lung function

C. **body mass index, obstruction [FEV1], dyspnea and exercise capacity**

D. heart disease, depression, and underweight status

E. smoking, pulmonary hypertension, and declining lung function

22. The combination of signs and symptoms of chronic bronchitis, emphysema, and reactive airway disease includes the following symptoms:

A. productive cough or acute chest illness, breathlessness, wheezing

B. high blood pressure, heart failure, high heart rate

C. breathlessness, wheezing, high BP

D. productive cough or acute chest illness, heart failure

E. heart failure, dyspnea, pulmonary hypertension, cor pulmonale, left-sided heart failure.

23. Define the main goals of COPD management:

A. preserving lung function at least at 55% level, optimal control of FEV1

B. preserving lung function at least at 80% level

C. improving life quality, preventing the recurrence of exacerbations

D. improving life quality, physical state

E. **preserving optimal lung function, improving symptoms, and preventing the recurrence of exacerbations**

24. The indications for intensive care admission are the following:

A. confusion, lethargy, respiratory muscle fatigue

B. increasing BP, active respiratory failure

C. worsening hypoxemia, and respiratory acidosis (pH <7,30), clinical concern for impending or active respiratory failure

D. **A, C right**

E. none of the above

25. How many stages of COPD management there are according to GOLD?

A. 3

B. **4**

C. 6

D. 5

E. 2

26. Most of the medications used are directed at the following 4 potentially reversible causes of airflow limitation, such as:

A. respiratory tract neoplasms, restrictive disorders, increased airway secretions, pulmonary edema

B. acute respiratory failure, pulmonary edema, heart failure, heart rhythm disturbances

C**. Bronchial smooth muscle contraction, bronchial mucosal congestion and edema, airway inflammation, increased airway secretions**

D. productive cough, acute chest illness, breathlessness, wheezing

E. restrictive disorders, increased airway secretions, acute chest illness, breathlessness

27. The main effects of bronchodilators on the respiratory system are:

A. **dilating airways, decreasing airflow resistance**

B. constricting airways, decreasing airflow resistance

C. dilating airways, increasing airflow resistance

D. constricting airways, increasing airflow resistance

E. dilating airways, decreasing blood pressure

28. What are the main groups of medications used for COPD treatment?

A. **Beta-2 agonists and anticholinergics, corticosteroid therapy, phosphodiesterase inhibitors, endogenous opioids, beta-blockers**

B. Beta-2 agonists and anticholinergics, corticosteroid therapy, phosphodiesterase inhibitors, diuretics

C. corticosteroid therapy, phosphodiesterase inhibitors

D. Beta-2 agonists and anticholinergics

E. Beta-2 agonists and anticholinergics, corticosteroid therapy, phosphodiesterase inhibitors, diuretics, antiarrhythmic drugs

29. The multidisciplinary approach to the pulmonary rehabilitation emphasizes the following:

A. Patient and family education, smoking cessation

B. Respiratory and chest physiotherapy, physical therapy with bronchopulmonary hygiene, exercise, and vocational rehabilitation

C. medical management, psychosocial support

D. All of the above

E. Answers A,B are correct

30. Type 2 diabetes mellitus consists of an array of dysfunctions, which cause hyperglycemia and result from:

A. inadequate insulin secretion

B. **resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion**

C. excessive or inappropriate insuline secretion, resistance to glucagon action

D. resistance to insulin action

E. excessive or inappropriate glucagon secretion, resistance to glucagon action, low insuline secretion

31. What are the complications of Type 2 diabetes ?

A. **microvascular, macrovascular, and neuropathic complications**

B. hypoglycemic coma, venous thrombosis, acute heart failure

C. hypoglycemic coma, peripheral neuropathy, microvascular complications

D. microvascular, macrovascular and renal complications

E. microvascular, macrovascular complications resulting in high blood pressure

32. The major risk factors for type 2 diabetes mellitus are:

A. age, weight, race, arterial hypertension

B. family history, history of previous impaired glucose tolerance

C. Smoking, atherogenic diet, alcohol intake

D. **answers A, B correct**

E. answers A,C correct

33. Prediabetes definition includes the following :

A. **fasting blood glucose level of 100-125 mg/dL or a 2-hour post-oral glucose tolerance test (post-OGTT) glucose level of 140-200 mg/dL**

B. fasting blood glucose level higher than 100-125 mg/dL or a 2-hour post-oral glucose tolerance test (post-OGTT) glucose level of 140-200 mg/dL

C. fasting blood glucose level of 100-125 mg/dL or a 2-hour post-oral glucose tolerance test (post-OGTT) glucose level lower than 140-200 mg/dL

D. fasting blood insulin level of 140-200 mg/dL or a 2-hour post-oral glucose tolerance test (post-OGTT) glucose level of 100-125 mg/dL

E. fasting blood glucose level lower than 100-125 mg/dL or a 2-hour post-oral glucose tolerance test (post-OGTT) glucose level lower than 140-200 mg/dL

34. Metabolic syndrome, thought to be due to insulin resistance, can occur in patients with overtly normal glucose tolerance, prediabetes, or diabetes. It is diagnosed when a patient has at least 3 of the following 5 conditions:

A. Acute chest pain, elevated triglyceride level, low level of high-density lipoprotein (HDL) cholesterol, elevated blood pressure, fasting glucose value of 100 mg/dL or higher.

B. Abdominal obesity, elevated triglyceride level, low level of high-density lipoprotein (HDL) cholesterol, decreased blood pressure, fasting glucose value of 100 mg/dL or higher.

C. Abdominal obesity, elevated triglyceride level, low level of high-density lipoprotein (HDL) cholesterol, elevated blood pressure, fasting glucose value less than 100 mg/dL.

D. **Abdominal obesity, elevated triglyceride level, low level of high-density lipoprotein (HDL) cholesterol, elevated blood pressure, fasting glucose value of 100 mg/dL or higher.**

E. Abdominal obesity, elevated high-density lipoprotein (HDL) level, low level of low-density lipoprotein (LDL) cholesterol, elevated blood pressure, fasting glucose value of 100 mg/dL or higher.

35. In the absence of the risk factors for prediabetes and diabetes in asymptomatic adults who are overweight, the ADA recommends the following actions:

A. testing for prediabetes and diabetes beginning at age 65 years. If results are normal, testing should be repeated at least every 3 years

B. testing for prediabetes and diabetes beginning at age 35 years. If results are normal, testing should be repeated at least every 3 years

C. testing for prediabetes and diabetes beginning at age 45 years. If results are normal, testing should be repeated at least every 2 years

D. testing for prediabetes and diabetes beginning at age 45 years. If results are normal, testing should be repeated at least every 5 years

E. **testing for prediabetes and diabetes beginning at age 45 years. If results are normal, testing should be repeated at least every 3 years**

36. Drug classes used for the treatment of type 2 diabetes include the following:

A. Beta-2 agonists and anticholinergics, corticosteroid therapy, phosphodiesterase inhibitors, diuretics

B. **Biguanides,Sulfonylureas,Meglitinide derivatives, Alpha-glucosidase inhibitors,Thiazolidinediones (TZDs)**

C. Biguanides,Sulfonylureas,Meglitinide derivatives, Beta-2 agonists and anticholinergics

D. Biguanides,Sulfonylureas,Beta-blockers, Alpha-glucosidase inhibitors, Thiazolidinediones (TZDs)

E. Biguanides,Sulfonylureas, Meglitinide derivatives, Alpha-glucosidase inhibitors, phosphodiesterase inhibitors, diuretics, Thiazolidinediones (TZDs)

37. When does the ADA recommends initiation of complications monitoring?

A. **at the time of diagnosis of diabetes mellitus**

B. 5 years after diagnosis of diabetes mellitus

C. 10 years after diagnosis of diabetes mellitus

D. by the time of clinical manifestation of the complications

E. in case of emergency situations

38. Guidelines from the American College of Clinical Endocrinologists for the prevention of type 2 diabetes mellitus in patients at risk recommend the following measures:

A. Patient and family education, use of warfarin in conjunction with aspirin and/or clopidogrel

B. Start dietary therapy, increase the intake of saturated fats, trans-fatty acids, and cholesterol

C. Weight reduction, proper nutrition, regular physical activity

D. cardiovascular risk factor reduction, aggressive treatment of hypertension and dyslipidemia

E. **answers C, D correct**

39. What age group of patients with diabetes has an increased risk for the development of geriatric conditions (eg, cognitive, vision, and hearing impairments; falls)?

A. young patients (manifestation of diabetes at the age of 25 or less)

B. middle aged patients between 35 to 45

C. patients with high LDL cholesterol level

D. patients with low blood pressure

E. Middle-aged and older adults

40. What is the best model of education for the patients with type 2 diabetes?

A. brief instructions and a few pamphlets for patients with satisfactory control, individual attention and education for patients with poorly controlled diabetes

B. diabetes education needs to be a lifetime exercise

C. for patients with poorly controlled diabetes, individual attention and education is superior to group education

D. answer A, B correct

E. Answers B, C correct

41. What indicators characterize the "ideal" carbohydrate metabolism?

A. blood glucose should be maintained at near-normal levels (preprandial levels of 90-130 mg/dL) and hemoglobin A1C [HbA1c] levels <7%

B. blood glucose should be maintained at near-normal levels (preprandial levels of higher than 130 mg/dL) and hemoglobin A1C [HbA1c] levels <7%

C. blood glucose should be maintained at near-normal levels (preprandial levels of 90-130 mg/dL) and LDL cholesterol levels <7%

D. blood glucose should be maintained at near-normal levels (preprandial levels of 90-130 mg/dL) and hemoglobin A1C [HbA1c] levels <15%

E. blood glucose should be maintained at near-normal levels (postprandial levels of 90-130 mg/dL) and hemoglobin A1C [HbA1c] levels <7%

42. The dietary modifications for type 2 diabetes are the following:

A. **Mediterranean-style diet, Trans-palmitoleate, Advanced glycation end products**

B. high-carbohydrate diet

C. high-protein diet

D. low-fat diet

E. all of the above

43. Which factor has the most influence on the type 2 diabetes prognosis?

A. blood pressure level control

B. **glucose level control**

C. glucose level control, amount of physical activity

D. control of smoking and daily alcohol intake

E. glucose level control, LDL cholesterol level management

44. The 2010 American Heart Association/American Stroke Association (AHA/ASA) guidelines for the primary prevention of stroke include the following recommendations for patients with diabetes:

A. low physical activity, regular blood pressure control

B. drug therapy with ACE inhibitors or ARBs, statin therapy

C. **Regular blood pressure control, diet, physical activity, drug therapy with ACE inhibitors or ARBs, statin therapy**

D. high intensity of physical activity combined with statin therapy

E. Regular blood pressure control, diet, physical activity

45. Carcinogenesis from tobacco use occurs through several mechanisms, including:

A. direct delivery of carcinogens to tissues

B. direct delivery of carcinogens to tissues, inflammation, and breakdown of physiological barriers

C. autoimmune inflammation

D. mechanical breakdown of physiological barriers

E. mechanical breakdown of physiological barriers

46. Ultraviolet radiation is a well-established carcinogen for both melanoma and nonmelanoma skin cancers. Most experts recommend the complex of protective measures, such as:

A. limiting exposure to the sun during peak hours (between 10 AM and 4 PM); using protective clothing, including hats and sunglasses; and using sunscreens with a sun protection factor (SPF) of 50 or greater, with agents

that work against both ultraviolet (UV) A and UVB radiation (eg, oxybenzone, avobenzone, titanium dioxide, or zinc oxide)

B. limiting exposure to the sun during peak hours (between 10 AM and 4 PM); using protective clothing, including hats and sunglasses; and using sunscreens with a sun protection factor (SPF) of 30 or greater, with agents that work against both ultraviolet (UV) A and UVB radiation (eg, oxybenzone, avobenzone, titanium dioxide, or zinc oxide**)**

C. limiting exposure to the sun during peak hours (between 10 AM and 4 PM); using protective clothing, including hats and sunglasses; and using sunscreens with a sun protection factor (SPF) of 30 or greater, with agents that work against both ultraviolet UVA

D. limiting exposure to the sun during peak hours (between 8 AM and 5 PM); using protective clothing, including hats and sunglasses; and using sunscreens with a sun protection factor (SPF)

E. limiting exposure to the sun during peak hours (between 11 AM and 2 PM); using protective clothing, including hats and sunglasses; and using sunscreens with a sun protection factor (SPF) of 50 or greater

47. Dietary recommendations from the American Cancer Society (ACS) include:

A. eating a variety of healthful foods, with 5 or more servings of vegetables and fruits per day; use of whole grains in preference to processed (refined) grains and sugars; limited consumption of white meats,

B. eating a variety of healthful foods, with 5 or more servings of vegetables and fruits per day; use of whole grains in preference to processed (refined) grains and sugars; limited consumption of fat

C. eating a variety of healthful foods, with 5 or more servings of vegetables and fruits per day; use of whole grains in preference to processed (refined) grains and sugars; limited consumption of red meats, especially processed meats and those high in fat

D. eating a variety of whole grains; limited consumption of red meats, especially processed meats and those high in fat

E. Mediterranean diet

48. Higher levels of physical activity have been associated with decreases in the risks of colon and breast cancers. The mechanism of the protective effect remains uncertain but may be related to:

A. effects on hormone levels

B. effects on immunity and prostaglandins level

C. involve inflammatory, epigenetic, or metabolic effects

D. effects on immunity, hormone levels, or prostaglandins

E. involve inflammatory, epigenetic, hormonal, or metabolic effects

49. Approximately 17% of cancers occurring worldwide may be attributed to an infectious etiology. The primary cancers are associated with viral infections, which include:

A.human papillomavirus, human T-cell lymphotropic virus -1, Epstein-Barr virus and HHV-8

B. human papillomavirus**,** hepatitis B **and** C **virus, human herpes virus,** human T-cell lymphotropic virus **-1,** Epstein-Barr virus **and HHV-8**

C. human papillomavirus, hepatitis A, B and C virus, human herpes virus, human T-cell lymphotropic virus -1, Epstein-Barr virus and HHV-8

D.human papillomavirus, hepatitis B and C virus, human herpes virus, human T-cell lymphotropic virus -1, Epstein-Barr virus and HHV-8, Helicobacter pylori

E. human immunodeficiency virus

50. Breast Cancer Screening can include different tests, of which clinical breast examination and mammography are commonly used. Most experts agree that screening mammography should be performed routinely in women between the ages of 50 and 69 years.The frequency of screening in this population is:

A. biennial

B. annual

C. not recommended in the absence of risk factors

D. not recommended in the absence of family history or other risk factors

E. discussion of screening with patients and shared decision-making

51. Since 1990, the mortality rate from breast cancer has been declining approximately 2% per year. The survival benefit from mammography was greater in women in the age:

A. between the ages of 40 and 49 years

B. older than 50 years

C. between the ages of 50 and 69 years

D. over the age of 70 years

E. aged 65 to 74 years

52. The Papanicolaou smear is the standard screening test for cervical cancer. All guidelines for cervical cancer screening recommend starting Pap smears at age:

A. between the ages of 40 and 49 years

B. 30 years or 10 years after the onset of sexual activity

C. 21 years or 3 years after the onset of sexual activity

D. over the age of 40 years

E. should be determined on an individual basis

53. Colon cancer screening can be performed using stool-based tests and endoscopic or radiologic examinations. The guaiac-based fecal occult blood test has been shown in clinical trials to reduce colon cancer mortality by up to 33% when done on an annual basis. Before test the patient should do:

A. avoid nonsteroidal anti-inflammatory drugs, corticosteroids, and high doses of vitamin C (>250 mg) for 24 hours before and during the testing period

B. avoid nonsteroidal anti-inflammatory drugs, red meat, and high doses of vitamin C (>250 mg) for 48 hours before and during the testing period

C. avoid nonsteroidal anti-inflammatory drugs, sweet meal, and high doses of vitamin C (>1000 mg) for 48 hours before and during the testing period, and samples should be collected from 3 consecutive stools

D. discussion of screening with patients and shared decision-making

E. avoid nonsteroidal anti-inflammatory drugs, red meat, and high doses of vitamin C (>250 mg) for 48 hours before and during the testing period, and samples should be collected from 3 consecutive stools.

54. Colon cancer screening can be performed using flexible sigmoidoscopy and colonoscopy. The recommended screening interval for flexible sigmoidoscopy is

A. every 3 years, start at age 50 years in individuals who are at average risk of colon cancer and to continue until the patient's life expectancy is less than 10 years

B. every 10 years, start at age 60 years in individuals who are at average risk of colon cancer and to continue until the patient's life expectancy is less than 10 years

C. every 5 years, start at age 50 years in individuals who are at average risk of colon cancer and to continue until the patient's life expectancy is less than 10 years

D. every 15 years, start at age 65 years in individuals who are at average risk of colon cancer and to continue until the patient's life expectancy is less than 10 years

E. every 8 years, start in individuals who are at average risk of colon cancer and to continue until the patient's life expectancy is less than 10 years

55. The mainstays of prostate cancer screening are measurement of prostate-specific antigen and digital rectal examination. Measurement of PSA can be affected by such factors as:

A. other than prostate cancer, and prostate biopsy

B. preceding digital rectal examination

C. other than prostate cancer, prostate biopsy, including benign prostatic hypertrophy, ejaculation, bacterial prostatitis, urinary retention, and use of medications such as 5-alpha reductase inhibitors

D. use of medications such as 5-alpha reductase inhibitors, ACE inhibitor/angiotensin receptor blockers, NSAID

E. none of mentioned above

56. Guidelines regarding screening for prostate cancer with PSA testing and digital rectal examination vary considerably. The American Cancer Society and American Urological Association recommend consideration such screening regimen:

A. at age 50 years for most men; annual PSA testing and digital rectal examination for all men who have a life expectancy of at least 10 years and who desire screening.

B. at age 40 years for most men; annual PSA testing and digital rectal examination for all men who have a life expectancy of at least 10 years and who desire screening

C. at age 60 years for most men and at age 55 years for men who are at increased risk of prostate cancer due to family history or ethnic background; annual PSA testing and digital rectal examination for all men who have a life expectancy of at least 10 years and who desire screening

D. at age 50 years for most men and at age 45 years for men who are at increased risk of prostate cancer due to family history or ethnic background; annual PSA testing and digital rectal examination for all men who have a life expectancy of at least 10 years and who desire screening

E. discussion of the risks and benefits of screening with the patient and individualizing decisions

57. Which HPV genotypes cause almost two thirds of all cervical cancers and cervical intraepithelial neoplasia 2 and 3?

A. HPV genotypes 6, 11, 16 and 18

B. HPV genotypes 6, 16 and 18

C. HPV genotypes 6, 11 and 18

D. HPV genotypes 16 and 18

E. HPV genotypes 6 and11

58. Which HPV genotypes are implicated in genital warts?

A. HPV genotypes 6, 11, 16 and 18

B. HPV genotypes 6, 16 and 18

C. HPV genotypes 6, 11 and 18

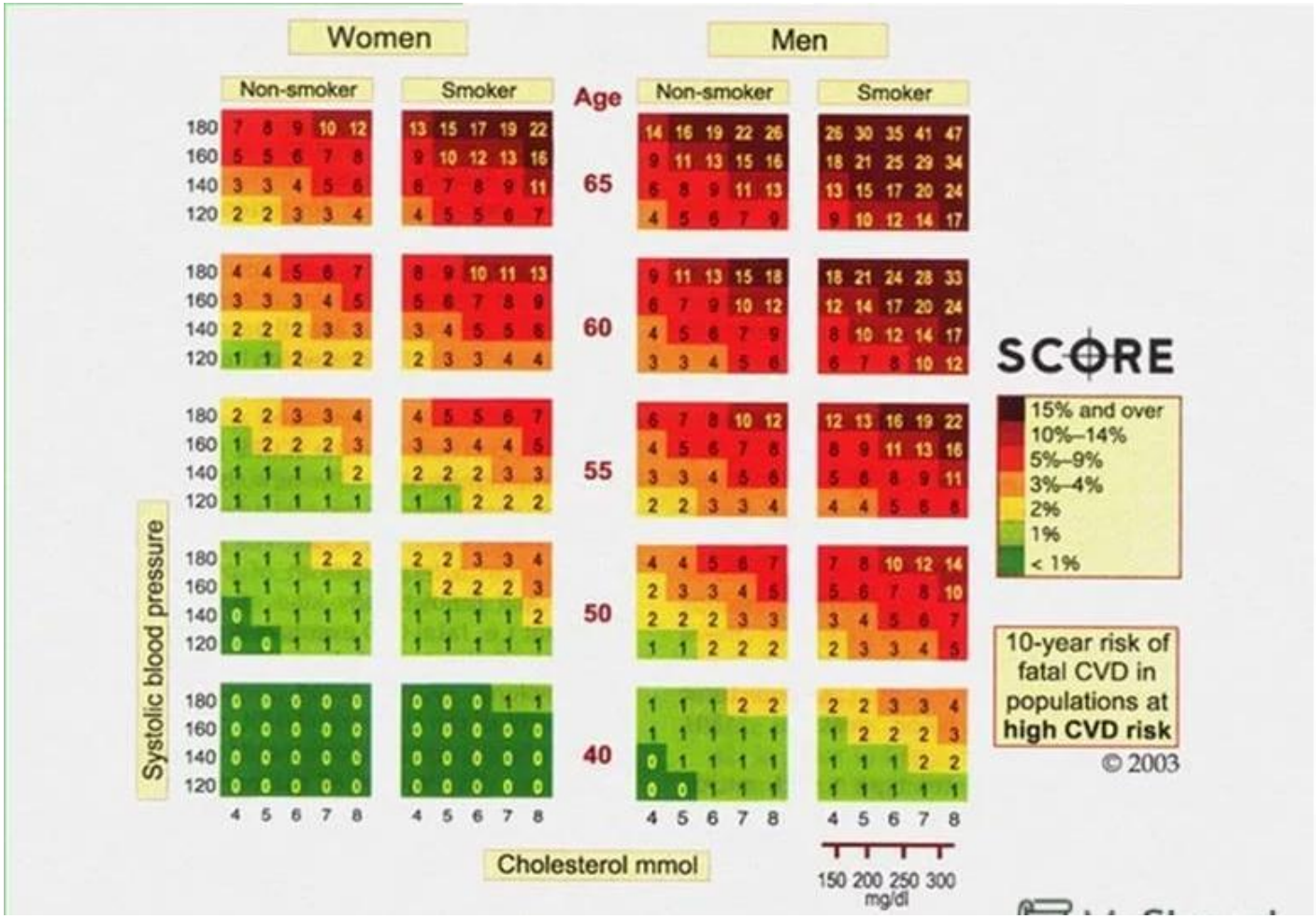
D. HPV genotypes 16 and 18

E. HPV genotypes 6 and 11

Appendice 1

SCORE

(Systematic Coronary Risk Evaluation)



Appendice 2

MODIFIED EHRA SCORE

Modified EHRA score	Symptoms	Description
1	None	AF does not cause any symptoms
2a	Mild	Normal daily activity not affected by symptoms related to AF[a]
2b	Moderate	Normal daily activity not affected by symptoms related to AF, but patient troubled by symptoms[a]
3	Severe	Normal daily activity affected by symptoms related to AF
4	Disabling	Normal daily activity discontinued

AF = atrial fibrillation; **EHRA** = European Heart Rhythm Association.

[a] EHRA class 2a and 2b can be differentiated by evaluating whether patients are functionally affected by their AF symptoms. AF-related symptoms are most commonly fatigue/tiredness and exertional shortness of breath, or less frequently palpitations and chest pain.

Appendice 3

CHA $_2$ DS $_2$ –VASC RISK FACTORS

CHA_2DS_2-VASc risk factor	Points
Congestive heart failure Signs/symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction	+1
Hypertension Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	+1
Age 75 years or older	+2
Diabetes mellitus Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin	+1
Previous stroke, transient ischaemic attack, or thromboembolism	+2
Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque	+1
Age 65–74 years	+1
Sex category (female)	+1

CHA $_2$ DS $_2$ -VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female).

Appendice 3

MODIFIABLE BLEEDING RISK FACTORS

Modifiable bleeding risk factors
Hypertension (especially when systolic blood pressure is >160 mmHg)[a,b,c]
Labile INR or time in therapeutic range <60%[a] in patients on vitamin K antagonists
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs[a,d]
Excess alcohol (≥8 drinks/week)[a,b]
Potentially modifiable bleeding risk factors
Anaemia[b,c,d]
Impaired renal function[a,b,c,d]
Impaired liver function[a,b]
Reduced platelet count or function[b]
Non-modifiable bleeding risk factors
Age[e] (>65 years)[a] (≥75 years)[b,c,d]
History of major bleeding[a,b,c,d]
Previous stroke[a,b]
Dialysis-dependent kidney disease or renal transplant[a,c]
Cirrhotic liver disease[a]
Malignancy[b]
Genetic factors[b]
Biomarker-based bleeding risk factors
High-sensitivity troponin[e]
Growth differentiation factor-15[e]
Serum creatinine/estimated CrCl[e]

HAS-BLED

ABC = age, biomarkers, clinical history; ATRIA = AnTicoagulation and Risk factors In Atrial fibrillation; CKD = chronic kidney disease; CrCl = creatinine clearance; HAS-BLED = hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly (1 point each); HEMORR $_2$ HAGES = hepatic or renal disease, ethanol abuse, malignancy, older (age >75), reduced platelet count or function, rebleeding risk (prior bleed; 2 points), hypertension (uncontrolled), anaemia, genetic factors (CYP 2C9 polymorphisms), excessive fall risk (including neuropsychiatric disease), and stroke; INR = international normalized ratio; ORBIT = Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; TTR = time in therapeutic range; VKA = vitamin K antagonist.

[a] Derived from the HAS-BLED score.

[b] Derived from the HEMORR $_2$ HAGES score.

[c] Derived from the ATRIA score.

[d] Derived from the ORBIT score.

[e] Derived from the ABC bleeding score.

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