Target Organ Disease in HTN

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PATHOLOGIC CONSEQUENCES OF HTN

- **HTN is an independent predisposing factor for:**

- **Hypertensive heart disease & Heart failure,**
- **Coronary artery disease,**
- **Stroke,**
- **Renal disease,**
- **Large vessel & Peripheral arterial disease (PAD).**

The complications of HTN:

- - Hypertensive (caused by the increased level of BP per se)
- - Atherosclerotic (caused by concomitant atherosclerosis),
- Both types of complications frequently coexist,

HEART

- **Most common cause of death in hypertensives is the Heart disease .**
- **Hypertensive heart disease is the result of structural and functional adaptations leading to:**

- **LVH,**
- **CHF,**
- **Abnormalities of blood flow (atherosclerotic CAD and microvascular disease),**
- **Cardiac arrhythmias.**

LVH:

- Individuals with LVH are at increased risk for:

- CHD,
- Stroke,
- CHF,
- Sudden death.

- Control of HTN can regress or reverse LVH and reduce the risk of CVD*.

CHF:

- **May be related to systolic or diastolic dysfunction, or combination of the two.**
- **Abnormalities of diastolic function that range from asymptomatic heart disease to overt HF are common in hypertensive patients.**
- **One-third of patients with CHF have normal systolic function but abnormal diastolic function.**
- **Diastolic dysfunction is an early consequence of HTN-related heart disease and is exacerbated by LVH and ischemia.**
- **Diastolic function can be evaluated most accurate by:**

- **Cardiac cath,**
- **Echocardiography,**
- **Radionuclide angiography.**

Classification of Hypertensive Heart Disease

- **Class I: Subclinical diastolic dysfunction by echo without LVH,**

(Asymptomatic abnormal LV relaxation/stiffness by Doppler echo, a common finding in hypertensives >65 years)

- **Class II: Left ventricular hypertrophy,**
  - **IIA: with normal functional capacity (NYHA Class I)**
  - **IIB: with abnormal functional capacity (NYHA Class >II)**
- **Class III: Heart failure with preserved ejection fraction (HFpEF)**
- **Class IV: Heart failure with reduced ejection fraction (HFrEF)**

Hypertensive Heart Disease

- **HTN may contribute to CAD more than is commonly realized:**
- **Hypertensives have more silent ischemia and unrecognized MIs,**
- **Patients with acute MI often have preexisting HTN that evaded detection or treatment.**

- **Assessment of BP is inaccurate during an ACS because of;**
- **Pain-induced BP rise, or**
- **Dysautonomia or pump failure that decreases BP.**

Preexisting HTN increases;

- **The case-fatality rate associated with an acute MI.**
- **The risk of hemorrhagic stroke during thrombolytic therapy, especially when systolic BP > 175 mm Hg.**

- **LVH with strain on the ECG is a serious harbinger of new-onset HF and death.**

- ***Cerebrovascular Disease***
- **HTN is a major risk factor for stroke and dementia.**

- **HTN accounts for 50% of strokes.**
- **In hypertensive persons,**
- **80% of strokes are ischemic (thrombotic or embolic)**
- **20% are hemorrhagic.**

- **HTN with asymptomatic carotid bruits should undergo Doppler ultrasonography.**
- **Older patients with ISH have a particular risk of stroke.**
- **Asymptomatic cerebral white matter lesions (WML) on MRI, likely accelerate the brain atrophy and vascular dementia that occur with aging, is common In middle-aged and elderly hypertensive patients.**

• Stroke:

- **Stroke** is the second most frequent cause of death in the world;
- It accounts for 5 million deaths each year,
- An additional 15 million persons having nonfatal strokes.
- Elevated BP is the strongest risk factor for stroke.
- 85% of strokes are due to infarction,
- The remainder are due to intracerebral or subarachnoid hemorrhage.
- The incidence of stroke rises progressively with increasing BP levels, particularly systolic BP in individuals >65 years.
- Treatment of HTN decreases the incidence of both ischemic and hemorrhagic strokes.

- **Cognitive impairment and dementia:**

- **HTN also is associated with impaired cognition in aging population,**
- **An association is between midlife HTN and late-life cognitive decline.**
- **HTN-related cognitive impairment and dementia;**
- **May be a consequence of a single infarct due to occlusion of a "strategic" larger vessel**
- **Or multiple lacunar infarcts due to occlusive small vessel disease resulting in subcortical white matter ischemia.**
- **HTN therapy has a beneficial effect on cognitive function.**

- **Encephalopathy:**

- **Cerebral blood flow remains unchanged over a wide range of arterial BP (mean arterial BP of 50–150 mmHg) through *autoregulation* of blood flow.**

- **In the clinical syndrome of malignant HTN, encephalopathy is related to failure of autoregulation of cerebral blood flow at the upper pressure limit, resulting in vasodilation and hyperperfusion.**

- **Signs and symptoms of hypertensive encephalopathy may include:**

- Severe headache,
- Nausea and vomiting ,
- Focal neurologic signs,
- Alterations in mental status.

- **Untreated, hypertensive encephalopathy may progress to:**

- Stupor,
- Coma,
- Seizures,
- Death within hours.

- **It is important to distinguish hypertensive encephalopathy from other neurologic syndromes that may be associated with HTN;**

- **Cerebral ischemia,**
- **Hemorrhagic or thrombotic stroke,**
- **Seizure disorder,**
- **Mass lesions,**
- **Pseudo tumor cerebri,**
- **Delirium tremens,**
- **Meningitis,**
- **Acute intermittent porphyria,**
- **Traumatic or Chemical injury to the brain,**
- **Uremic encephalopathy.**

- ***Chronic Kidney Disease***

- **HTN is a risk factor for CKD.**
- **Typical pathologic change of small, scarred kidneys,**
- **Resulting from chronic exposure of the renal parenchyma to excessive pressure and flow,**
- **Is the most common cause of end-stage renal disease among blacks (hypertensive nephrosclerosis) .**

- **A spot urine collection should be obtained for;**

1- GFR and

2- Urinary albumin excretion,

Microalbuminuria (urine albumin–to–urine creatinine ratio of 30 to 300 mg/g) is a:

- **Sensitive early marker of kidney damage,**
- **Powerful independent predictor of CV complications from HTN,**
- **It reflects systemic vascular disease.**

- **The kidney is both a target and a cause of HTN.**

- **Cause;**

- Primary renal disease is most common etiology of secondary HTN.

- **Mechanisms of kidney-related HTN include:**

- Diminished capacity to excrete sodium,

- Excessive renin secretion in relation to volume status,

- Sympathetic nervous system overactivity.

- **Target;**
- **HTN is a risk factor for renal injury and ESRD.**
- **Renal risk more closely related to systolic than to diastolic BP,**
- **Black men are at greater risk than white for ESRD at every level of BP.**
- **Glomerular injury may be a consequence of direct damage to the glomerular capillaries due to glomerular hyperperfusion.**
- **Atherosclerotic, HTN-related vascular lesions in the kidney;**

- **Primarily affect preglomerular arterioles,**
- **Resulting in ischemic changes in the glomeruli and postglomerular structures.**

- **The renal lesion associated with malignant HTN consists of:**

- Fibrinoid necrosis of the afferent arterioles,
- Sometimes extending into the glomerulus,
- May result in focal necrosis of the glomerular tuft.

- **Macroalbuminuria (random urine albumin/creatinine ratio >300 mg/g) or microalbuminuria (random urine albumin/creatinine ratio 30–300 mg/g) are:**

- Early markers of renal injury,
- Risk factors for renal disease progression,
- Risk factors for cardiovascular disease.

- **Renal damage In HTN dramatically increases the risk of a cardiovascular event.**
- **Most patients with HTN-associated CKD die of heart attack or stroke before renal function deteriorates sufficiently to require chronic hemodialysis.**

- ***Large-Vessel Disease***

- **HTN is a major risk factor for:**
- **- Aortic dissection (distal more than proximal dissection),**
- **- Abdominal aortic aneurysm, (AAA)**
- **- Peripheral arterial disease.**

- **One-time abdominal ultrasound screening for AAA is recommended after the age of 65 years in:**

- **Smokers**
- **In those with severe systolic HTN,**
- **If aortic pulsations are detected below the umbilicus,**

PERIPHERAL ARTERIES

- **In addition to contributing to the pathogenesis of HTN, blood vessels are a target organ for atherosclerotic disease secondary to long-standing elevated BP.**

- **In HTN, vascular disease is a major contributor to;**

- Stroke,

- Heart disease,

- Renal failure.

- **Hypertensives with arterial disease of the lower extremities are at increased risk for future cardiovascular disease.**
- **Patients with stenotic lesions of the lower extremities;**

- May be asymptomatic,

- Intermittent claudication is the classic symptom of PAD.

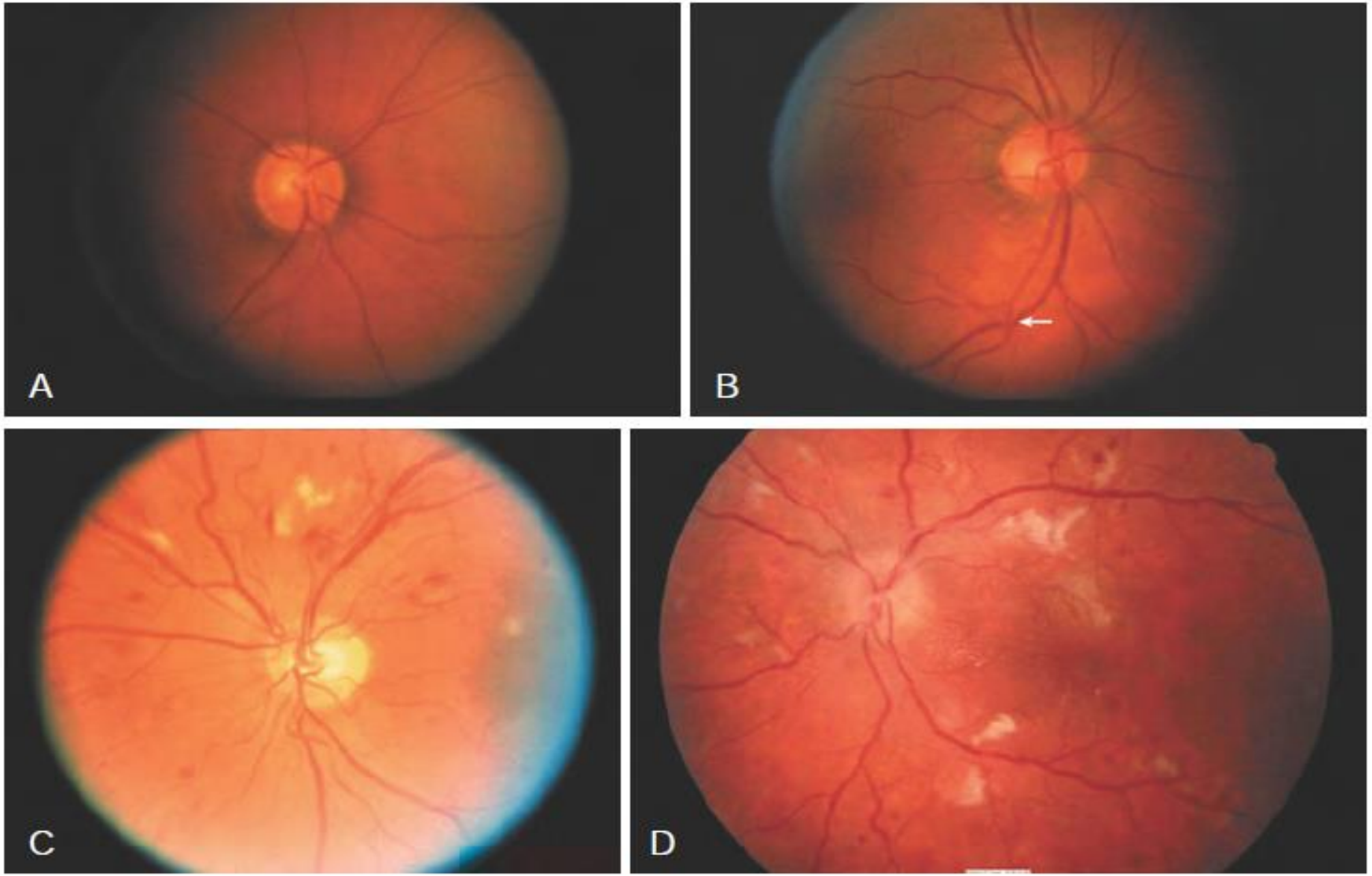
- The ankle-brachial index is a useful approach for evaluating PAD;

- (the ratio of noninvasively assessed ankle to brachial systolic BP).

- An ABI <0.90 is diagnostic of PAD and is associated with >50% stenosis in at least one major lower limb vessel.
- An ABI <0.80 is associated with elevated BP, particularly systolic BP.

- **ERECTILE DYSFUNCTION.**
- **Self-reported erectile dysfunction occurs in more than half of men with HTN and independently predicts fatal and nonfatal cardiovascular events.**

- Retinal photographs showing the stages of HTN retinopathy.
- A, Mild diffuse arteriolar narrowing. B, Arterial-venous nicking.
- C, Hemorrhages and exudates. D, Papilledema.

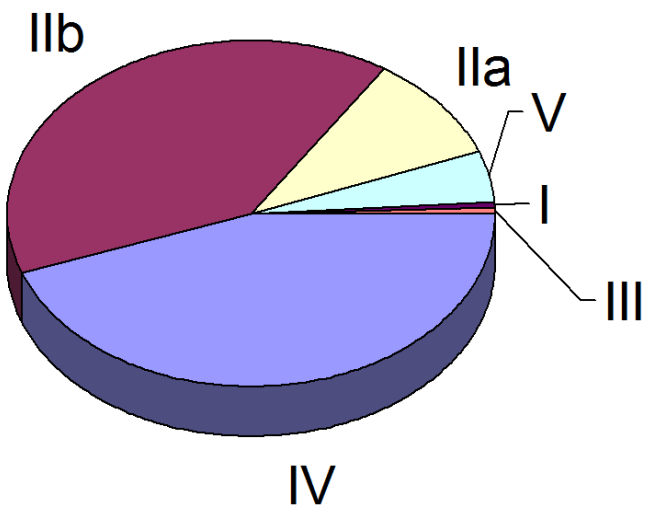


Factors Influencing Prognosis in Patients with HTN

Risk Factors for Cardiovascular Disease
Increased systolic and diastolic blood pressure levels
Increased pulse pressure (in the elderly)
Age: men, > 55 years; women, > 65 years
Smoking
Dyslipidemia (LDL cholesterol > 115 mg/dL)
Impaired fasting glucose (102-125 mg/dL) or abnormal glucose tolerance test result
Family history of premature cardiovascular disease
Abdominal obesity
Diabetes mellitus
Subclinical Target Organ Damage
Left ventricular hypertrophy
Carotid wall thickening or plaque
Low estimated glomerular filtration rate ≤ 60 mL/min/1.73 m^2
Microalbuminuria
Ankle-brachial index < 0.9
Established Target Organ Damage
Cerebrovascular disease: ischemic stroke, cerebral hemorrhage, transient ischemic attack
Heart disease: myocardial infarction, angina, coronary revascularization, heart failure
Renal disease: diabetic nephropathy, renal impairment
Peripheral arterial disease
Advanced retinopathy: hemorrhages or exudates, papilledema

Hyperlipidemia

Fridrecksen's classification of hyperlipidemias



Phenotype	TC	TG	Lipoproteins
I	↑	↑	↑ Chylomicrons
IIa	↑ →	→	↑ LDL
IIb	↑	↑	↑ **LDL,** ↑**VLDL**
III	↑	↑	↑ **IDL**
IV	→	↑	↑**VLDL**
V	↑ →	↑	↑ Chylomicrones ↑**VLDL**

Clinical manifestations of Atherosclerotic Vascular Disease

Vascular basin	Acute manifestation	Chronic manifestation
Coronary arteries	**Acute coronary syndromes:** - **unstable angina** - **AMI** - **sudden cardiac death**	**Stable angina** **Vasospastic angina**
Carotid and cerebral arteries	**Transient ischemic attack** **Stroke**	**Chronic cerebral ischemia ("discirculatory encephalopathy")**
Aorta	**Aortic dissection**	**Aortosclerosis** **Aortic aneurysm**
Mesenteric arteries	**Mesenteric thrombosis**	**Chronic intestinal ischemia ("abdominal angina")**
Renal arteries	**Cholesterol emlolism of renal artery**	**Renovascular hypertension** **Renal failure**
Pelvical and lower extremities arteries	**Acute limb ischemia**	**Erectile dysfunction** **Lerish syndrome** **Chronic limb ischemia (intermittent claudication)**

Hypertriglyceridemia-induced acute pancreatitis

- — **Hypertriglyceridemia (HTG) is an important cause of acute pancreatitis.**
- **Early clinical recognition of HTG-induced pancreatitis (HTGP) is important to provide appropriate therapy and to prevent further episodes.**

- **Mild** (150 to 199 mg/dL 1.7 to 2.2 mmol/L)
- **Moderate** (200 to 999 mg/dL, 2.3 to 11.2 mmol/L)
- **Severe HTG** (1000 to 1999 mg/dL, 11.3 to 22.5 mmol/L)
- **Very severe** HTG (≥2000 mg/dL, >22.6 mmol/L)
- HTG is considered a significant risk for acute pancreatitis when levels are >1000 mg/dL.

- **Prevalence — Hypertriglyceridemia-induced pancreatitis (HTGP) causes**
- **1 to 14% of all cases of acute pancreatitis, and**
- **up to 56% of pancreatitis cases during pregnancy.**

- **Demographic differences between HTGP and other causes of pancreatitis;**
- **In a 400 consecutive cases of acute pancreatitis, patients with HTGP were;**
- **Younger in age (44 versus 52 years),**
- **Male Predominant (65 versus 45 percent),**
- **Obese (57 percent versus 34 percent),**
- **Diabetic (38 versus 17 percent).**

- **Risk of acute pancreatitis —**
- **Mild hypertriglyceridemia is associated with a low risk of acute pancreatitis.**
- **The risk increases progressively with serum triglyceride levels > 500 mg/Dl.**
- **the risk increasing markedly with levels > 1000 mg/dL.**
- **The risk of developing acute pancreatitis is approximately;**
- **5% with serum triglycerides >1000 mg/dL,**
- **10 to 20% with triglycerides >2000 mg/dL.**

- **ETIOLOGY —**
- **Both primary (genetic) and secondary disorders of lipoprotein metabolism are associated with hypertriglyceridemia-induced pancreatitis (HTGP).**

- **A- Primary hypertriglyceridemia —**
- **Types I (high chylomicrons),**
- **IV (high very low-density lipoprotein [VLDL]), and**
- **V (high chylomicrons and VLDL) dyslipidemias**
- **Associated with severe hypertriglyceridemia (HTG) and an increased risk of acute pancreatitis.**

- **B- Secondary hypertriglyceridemia —**
- **Various conditions can raise triglycerides and lead to HTGP.**

- 1- **Diabetes mellitus** –
- **Poorly controlled diabetes mellitus (types 1 and 2) and diabetic ketoacidosis can trigger HTGP.**
- **Pancreatitis in diabetic ketoacidosis (DKA) usually occurs with severe metabolic acidosis characterized by a low serum pH (<7.1) and high anion gap.**
- **Marked elevation of serum triglycerides occurs during episodes of DKA.**

- 2- **Medications** –
- **Hormone supplementation with estrogen and selective estrogen receptor modulator, tamoxifen, can raise serum TG levels.**
- **Other medications associated with elevated serum triglyceride levels include;**

- **Clomiphene,**
- **Protease inhibitors,**
- **Antiretroviral agents,**
- **Propofol,**
- **Olanzapine,**
- **Mirtazapine,**
- **Retinoids,**
- **Thiazide diuretics,**
- **Beta-blockers.**

- 3- **Pregnancy** –
- **Although pregnancy causes an increase in serum TG that peaks in the third trimester, the total serum TG level rarely exceeds 300 mg/dL, a concentration that is not sufficient to cause acute pancreatitis.**
- **Cases of nongenetic, nonfamilial pregnancy-induced HTG have been reported but are rare.**
- **Most cases of HTGP that occurs during pregnancy are attributable to underlying familial HTG.**

- 4- **Alcohol** –
- **In a study of approximately 8000 men and women, the prevalence of serum TG concentrations above 227 mg/dL increased from 8 to 20% with an increase in alcohol intake from 3-9 or more drinks per day.**
- **The TG elevations with alcohol intake are transient and likely to be an epiphenomenon rather than a cause of pancreatitis.**

- 5- **Hypothyroidism** –
- **Hypothyroidism is associated with hypertriglyceridemia,**
- **In rare cases can be severe enough to result in HTGP.**

- **PATHOGENESIS —**
- **Triglycerides themselves do not appear to be toxic.**
- **Rather, it is the breakdown of triglycerides into toxic free fatty acids (FFA) by pancreatic lipases that is the cause of lipotoxicity during acute pancreatitis.**

- **The severity of acute pancreatitis in patients with HTG is dependent on both:**
- **The inflammatory response caused by pancreatitis itself,**
- **the injury caused by lipotoxicity from triglyceride hydrolysis.**
- **In most cases, the HTG is transient and returns to near normal within two to three days, depending on etiology.**

- **MANAGEMENT —**
- **Management of patients with HTGP includes:**

- **Treatment of acute pancreatitis, and**
- **Reduction of serum TG levels with the goal of preventing necrotizing pancreatitis and organ failure.**

- **Treatment of acute pancreatitis —**
- **Initial management of a patient with acute pancreatitis consists of supportive care with;**

- **Fluid resuscitation,**
- **Pain control, and**
- **Nutritional support.**

- **Initial therapy for hypertriglyceridemia- Choice of therapy —**
- **The main treatment modalities for initial management of HTG are apheresis and insulin.**
- **Our approach to initial therapy for hypertriglyceridemia in patients with HTGP is based on the severity of acute pancreatitis and the presence of worrisome clinical features**

- SUMMARY AND RECOMMENDATIONS
- ●Hypertriglyceridemia (HTG) is one of the most common causes of acute pancreatitis.
- It is reported to cause 1 to 14% of all cases of acute pancreatitis and up to 56% of cases during pregnancy. The risk of developing acute pancreatitis is approximately 5% with triglycerides >1000 mg/dL and 10 to 20% with triglycerides >2000 mg/dL.
- ●Primary (genetic) and secondary disorders of lipoprotein metabolism are associated with hypertriglyceridemia-induced pancreatitis (HTGP). Triglycerides themselves do not appear to be toxic. Rather, it is the breakdown of triglycerides into toxic free fatty acids by pancreatic lipases that is the cause of lipotoxicity during acute pancreatitis.
- ●The initial clinical presentation of HTGP is similar to that of acute pancreatitis due to other causes; abdominal pain, nausea, and vomiting are the major complaints.
- Physical examination findings suggestive of underlying hypertriglyceridemia include eruptive xanthomas over the extensor surfaces of the arms, legs, buttocks, and back, hepatosplenomegaly from fatty infiltration and lipemia retinalis.
- ●HTGP should be suspected in patients with acute pancreatitis and risk factors for hypertriglyceridemia.
- Risk factors for hypertriglyceridemia include poorly controlled diabetes, alcoholism, obesity, pregnancy, prior pancreatitis, and a personal or family history of hypertriglyceridemia. Serum triglyceride levels >1000 mg/dL are required for hypertriglyceridemia to be considered the underlying etiology of acute pancreatitis.

- ●Initial management of patients with HTGP includes treatment of acute pancreatitis and reduction of serum triglyceride levels to <500 mg/Dl.
- ●In patients with HTGP (serum triglyceride level >1000mg/dL plus lipase >3 times the upper limit of normal) and signs of hypocalcemia, lactic acidosis, signs of worsening systemic inflammation or organ dysfunction, or multi-organ failure, we suggest treatment with apheresis, and specifically therapeutic plasma exchange. Triglyceride levels should be monitored every cycle of apheresis.
- We continue apheresis until triglyceride levels are below <500 mg/dL.
- ●In patients without worrisome features, we suggest initiating therapy with intravenous (IV) regular insulin . We administer insulin at a rate of 0.1 to 0.3 units/kg/hour. In patients with blood sugar levels between 150 and 200 mg/dL, we administer IV glucose supplementation with a separate 5% dextrose infusion to prevent hypoglycemia. Triglyceride levels should be monitored every 12 hours. Serum glucose should be measured every hour and the insulin/5% dextrose infusion should be adjusted accordingly. Intravenous insulin should be stopped when triglyceride levels are <500 mg/dL.
- ●Once triglyceride levels are <500 mg/dL, patients with HTGP require long-term therapy to prevent recurrent pancreatitis and to prevent other complications of HTG. This consists of both pharmacologic therapy (eg, oral gemfibrozil 600 mg twice daily) and dietary modification (eg, fat- and simple sugar-restricted diet).
- Other nonpharmacologic interventions include weight loss in obese patients, aerobic exercise, avoidance of concentrated sugars and medications that raise serum triglyceride levels, and strict glycemic control in diabetics.
- ●Patients with HTGP should be evaluated for secondary causes of hypertriglyceridemia.
- For patients with hypertriglyceridemia not clearly associated with a secondary cause, family members should be screened with a fasting triglyceride level.