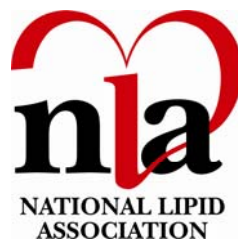


Core Curriculum  
in  
Clinical Lipidology

by the



Approved June 1, 2008

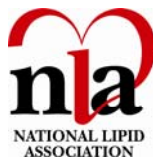
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## Introduction

The National Lipid Association (NLA), in conjunction with the American Board of Clinical Lipidology (ABCL) and the Accreditation Council of Clinical Lipidology (ACCL), approved in May 2008, a Core Curriculum in Clinical Lipidology. This curriculum identifies and defines areas of knowledge important to the delivery of quality care and serves as a basis for the content of the certification examinations in Clinical Lipidology. The core curriculum is comprised of the information deemed as the most relevant clinical information for a practicing lipid specialist or lipidologist. The NLA will provide appropriate study tools and courses based on the curriculum to assist members in preparing to meet certification requirements. This curriculum is intended to be a working document that will evolve along with the science and treatment guidelines in the field.

The content of the Core Curriculum was used as the basis for the NLA Self-Assessment Program (NLA-SAP) and other training courses developed by NLA.

**Revision process:** The Curriculum is intended to be revised on a two year basis. The Core Curriculum developers will consider new evidence in the peer-reviewed literature, as well as input from the certification boards.



# Core Curriculum in Clinical Lipidology

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## **CORE CURRICULUM IN CLINICAL LIPIDOLOGY**

### **PART I: BASIC LIPID AND LIPOPROTEIN METABOLISM DIAGNOSIS AND TREATMENT OF DYSLIPIDEMIA**

#### **A. Lipid and Lipoprotein Metabolism**

- a. Lipids
  - i. Fatty acids
  - ii. Cholesterol
  - iii. Triglyceride
  - iv. Cholesteryl ester
  - v. Phospholipids
  - vi. Beta-hydroxybutyrate and acetoacetate
  - vii. Lipoprotein-X
- b. Lipoprotein Composition
  - i. Chylomicrons
  - ii. VLDL
  - iii. LDL
  - iv. HDL
  - v. Chylomicron and VLDL Remnants
  - vi. Lipoprotein (a)
- c. Apolipoproteins
  - i. Apo B48
  - ii. Apo B100
  - iii. Apo CII
  - iv. Apo CIII
  - v. Apo AI
  - vi. Apo AII
  - vii. Apo AV
  - viii. Apo E
  - ix. Apo V
- d. Enzymes Involved in Lipoprotein Metabolism
  - i. Lipoprotein Lipase
  - ii. Hepatic Lipase
  - iii. LCAT
  - iv. ACAT
  - v. CETP
  - vi. PLTP
  - vii. Lp PLA<sub>2</sub>
  - viii. DGAT2
  - ix. MTP
  - x. Endothelial lipase

- e. Lipoprotein Measurements
  - i. Friedewald Formula
  - ii. Non-HDL cholesterol
  - iii. Direct LDL cholesterol
  - iv. Apo B
  - v. LDL Particle Concentration
  - vi. Triglycerides
  - vii. Gradient gel electrophoresis/VAP/NMR Lipoprofile methodology
  - viii. Other HDL Categorizations
    - 1. A1
    - 2. All particles vs. A1
    - 3. Etc.
  - ix. Ratios
- f. Exogenous Lipoprotein Metabolism
  - i. Formation of Chylomicrons
  - ii. Lipolysis of Chylomicrons
  - iii. Chylomicron Remnant Uptake
  - iv. Postprandial Lipemia
- g. Endogenous Lipoprotein Metabolism
  - i. VLDL Synthesis and Secretion
  - ii. VLDL Conversion to IDL
  - iii. IDL Conversion to LDL
  - iv. LDL Uptake by LDL Receptor
  - v. LDL Receptor Structure
  - vi. PCSK9
- h. HDL Metabolism
  - i. Efflux of Free Cholesterol Mediated by ABCA1
  - ii. ABCG1/G4 Interaction with HDL
  - iii. Speciation of HDL
  - iv. Interaction with HDL by SRB1 and Other Receptors
  - v. Cholesterol Ester Transfer Protein – Action of Cholesterol Esters and Triglyceride Transfer Among Lipoproteins
  - vi. Pre-beta HDL (nascent HDL)
  - vii. Apo A1, A11, Apo E
  - viii. HDL3, HDL2, HDL1

## **B. Genetic Disorders of Lipoprotein Metabolism**

- a. Genetic Causes of Elevated LDL
  - i. Familial Hypercholesterolemia
  - ii. Familial Combined Hyperlipidemia
  - iii. Familial Defective Apo B
  - iv. Familial Autosomal Recessive Hypercholesterolemia
    - 1. Due to defect in chromosome 1p35-36

- b. PCSK9 Defects
    - i. Gain of function defects
      - 1. Increased LDL and early CAD
    - ii. Loss of function defects
      - 1. Decreased LDL and reduced CAD Risk
  - c. Genetic Causes of low LDL
    - i. Hypobetalipoproteinemia
    - ii. Abetalipoproteinemia
  - d. Genetic Causes of Elevated Triglycerides
    - i. Fasting Chylomicronemia Syndrome
      - 1. Lipoprotein Lipase or Apo CII deficiency
    - ii. Familial Hypertriglyceridemia
    - iii. Familial Dysbetalipoproteinemia
    - iv. FCHL
  - e. Failure of Chylomicron Production
    - i. Chylomicron Retention Disease
  - f. Elevated Lp(a)
    - i. Difficulties with assay
  - g. Genetic Causes of Low HDL
    - i. Familial Hypoalphalipoproteinemia
    - ii. Tangier Disease
    - iii. LCAT related disorders
      - 1. LCAT deficiency
      - 2. Fish eye disease
  - h. Lysosomal Acid Lipase Disorders
    - i. Cholesterol Ester Storage Disease
    - ii. Wolman's Disease
- C. CV Risk Assessment**
- a. Family History
  - b. Physical Exam Findings
  - c. Gender Effects
    - i. Menopausal Effects on Lipid Levels and Atherosclerosis
      - 1. Exogenous hormones in premenopausal era
    - ii. Polycystic ovary syndrome
    - iii. Male Hypogonadism
  - d. Framingham Risk Score
    - i. Traditional
    - ii. ATP III
    - iii. Reynolds Risk Score
    - iv. International Scores
  - e. Effects of Smoking on Lipid Metabolism and Atherosclerosis
  - f. Effects of Hypertension on CV Risk
    - i. The Lipid Altering and Atherosclerotic Effect of Anti-hypertensive therapy

- g. Diabetes – Type 1 and Type 2
  - i. Mechanisms of Dyslipidemia and Increased Atherosclerosis in DM
  - ii. Lipid Effects of Diabetes Therapies
  - iii. Atherosclerotic Effects of Diabetes Therapies
- h. Definition of Clinically Significant Atherosclerosis
- i. Metabolic Syndrome and CV Risk
  - i. Cardiometabolic risk definition
- j. Coronary calcium detection
- k. Noninvasive assessments of atherosclerosis for risk assessment and treatment follow-up

#### **D. Secondary Causes of Dyslipidemia**

- a. Hypothyroidism
- b. Drugs
  - i. Thiazide Diuretics
  - ii. Beta-Blockers
  - iii. Glucocorticoids
  - iv. Sex hormones
  - v. Retinoic Acid derivations
  - vi. Antipsychotics
  - vii. Antiretrovirals
  - viii. Immunosuppressive agents
  - ix. Etc.
- c. Obesity
- d. Type 2 Diabetes
- e. Nephrotic syndrome
  - i. Renal disease
  - ii. HIV
- f. ESRD
- g. PCOS
- h. Transplant
- i. Kawasaki

#### **E. ATP III Guidelines**

- a. Risk Categorizations and Determination of Goals for LDL-C and Non-HDL-C
- b. Initiation of Non-pharmacological and Pharmacological Therapy
- c. Non-pharmacological Treatment
- d. Initiation of Pharmacological Therapy

#### **F. Non-Pharmacological Management of Dyslipidemia and Therapeutic Lifestyle Changes (TLC)**

- a. Low Saturated Fat, Low Cholesterol Diet
- b. Na and Salt Control
- c. Viscous or Soluble Fiber
- d. Plant Sterols and Stanols
  - i. Effect of Esterification
- e. Foods Rich in Omega-3 Fatty Acids

- f. Exercise
- g. Weight Management
- h. Behavior Modification
- i. Smoking Cessation
- j. Supplements/Nutraceuticals/OTC therapies
  - i. Supplements that don't work
    - 1. Policosanol
  - ii. Supplements that may work
    - 1. Red yeast rice
    - 2. Cinnamon
    - 3. Garlic
- k. Alternative therapies

## **G. Mechanism of Action, Pharmacokinetics, Side Effects, Safety and Efficacy of Pharmacological Therapy**

- a. Statins
- b. Niacin
- c. Fibrates
- d. Bile Acid Sequestrants
- e. Omega-3 Fatty Acids
- f. Cholesterol absorption Inhibitors
- g. Approved Weight Loss Drugs
  - i. Sibutramine
  - ii. Orlistat
- h. Weight Loss Drugs in Development
  - iii. Endocannabinoid Receptor Blockers
- i. Combination Therapy

## **H. Pharmacological Therapy for Dyslipidemia**

- a. Elevated LDL
- b. Combined Dyslipidemia (LDL and VLDL)
- c. Low HDL
- d. Elevated Triglycerides

## **I. Internet Resources for Clinicians**

## **J. Consultative Issues in Clinical Lipidology**

# **PART II: ATHEROSCLEROSIS, MANAGEMENT OF CARDIOMETABOLIC RISK, BIOMARKERS, EPIDEMIOLOGY AND STATISTICS, CLINICAL TRIALS**

## **A. Atherosclerosis**

- a. Normal Arterial Development
  - i. Pre-natal development of arteries
  - ii. Diffuse intimal thickening as post-natal phenomenon
  - iii. Longitudinal mechanical stress in coronaries and at branch points

- b. Sequence of Atherosclerotic Lesions
  - i. Diffuse intimal thickening
  - ii. Fatty streak
  - iii. Fibrous plaque
  - iv. Plaque rupture or erosion
  - v. Organization of mural thrombus
  - vi. Calcification
  - vii. Neovascularization
  - viii. Foam cell formation
- c. Lipoproteins in the arterial wall
  - i. Lack of lymph vessels in the intima
  - ii. Retention of LDL
  - iii. Fusion of LDL to form droplets and vesicles
  - iv. LDL oxidation and action of phospholipases
  - v. Interaction of HDL with macrophages
- d. Role of arterial wall cells
  - i. Endothelium
  - ii. Smooth muscle cells
  - iii. Inflammatory cells

## **B. Biomarkers of Atherosclerosis**

- a. Lipoprotein Related
  - i. Lipids (from lipid profile) and ratios [LDL-C, non-HDL-C, TC/HDL-C, non-HDL-C/HDL-C, etc]; concentration of atherogenic lipoproteins [apo B, LDL particle size, LDL particle concentration]
  - ii. HDL
  - iii. Lp(a)
  - iv. Clinical Evaluation for genetic and secondary causes of dyslipidemia
- b. Inflammatory markers and other Blood Tests
  - v. hs-CRP
  - vi. Lp-PLA2
  - vii. Emerging Assays
  - viii. Myeloperoxidase

## **C. Management of Cardiometabolic Risk**

- a. Pathology of Visceral Adiposity
  - i. Adipokines
    - 1. Leptin
    - 2. Adiponectin
    - 3. Resistin
    - 4. IL-6
    - 5. TNF-alpha
  - ii. Non- Adipokines
    - 1. Ghrelin
- b. Endocannabinoid System
- c. Metabolic Syndrome
  - i. Definition



- ii. Pathogenesis of the Metabolic Syndrome
  - 1. Appetite regulation
  - 2. Adipocyte and triglyceride/fatty acid metabolism
  - 3. Hepatic handling in increased triglyceride load
  - 4. Role of visceral adipose tissue in genesis of hypertension
- iii. Consequences of the Metabolic Syndrome
- iv. Treatment Guidelines
  - 1. Targets for Treatment
  - 2. Lifestyle Modification and Weight Management Strategies
  - 3. Medical Treatment
  - 4. Polypharmacy in the Treatment of Metabolic Syndrome
- d. Diabetic Dyslipidemia
- e. Non-alcoholic fatty liver disease

#### **D. Epidemiology and Statistics**

- a. Mean and Median
- b. Measures of Variability
  - i. The Normal Distribution
  - ii. Percentiles
- c. Data Acquisition
  - i. Random Sampling
  - ii. Bias
  - iii. Observational Studies
  - iv. Randomized Clinical Trials
  - v. Meta-analyses
- d. Estimating the Mean and Standard Deviations from a Sample
- e. Unpaired and paired t-tests
- f. Analyzing Rates and Proportions
  - i. Chi-Square Applications to Experiments with More Than two Treatments or Outcomes
    - 1. Subdividing Contingency Tables
  - ii. The Fisher Exact Test
- g. Determining a Test's Power
  - i. Size of the Type I error  $\alpha$
  - ii. Size of the Treatment Effect
  - iii. Population Variability
  - iv. Sample Sizes
- h. Power and Sample Size for Analysis of Variance
- i. Odds Ratios, relative risks, absolute risks, attributable risks, number needed to treat/harm, Cox hazard ratio, Kaplan Meier Plots, etc.
- j. Non-inferiority trial designs
- k. Regression

#### **E. Clinical Trials**

- a. Overview of Key Lipid Trials

## **PART III: COMPLEX CASE MANAGEMENT AND ADVANCED PHARMACOLOGY**

### **A. Management of Dyslipidemia in Special Populations**

- a. Women
  - i. Postmenopausal Hormonal Therapy Effects on Lipoproteins, Thrombosis & Atherosclerosis; PCOS/OCP issues
- b. Elderly
- c. Children
- d. Diabetes and Metabolic Syndrome
- e. Acute Coronary Syndromes
- f. Transplant Recipients
- g. Chronic Renal Disease
- h. HIV Patients
- i. Ethnic Groups
  - i. African Americans
  - ii. Hispanics
  - iii. Native Americans
  - iv. Pacific-Islanders
  - v. Asian Indians/South Asians
  - vi. Asians
- j. Healthcare Disparity
  - i. Education
  - ii. SES
  - iii. Insurance
  - iv. Ethnicity
  - v. Urban vs. Rural

### **B. Experimental Therapies**

- a. Targeting (reducing) atherogenic lipoproteins [squalene synthase inhibitors, MTP inhibitors, antisense oligonucleotides to Apo B]
- b. Targeting HDL [CETP inhibitors, Apo A-I Milano, LUVs, etc.]
- c. Targeting the vessel wall [antiatherosclerotic and anti-inflammatory therapies]

### **C. Other Treatments**

- a. LDL Apheresis

## **PART IV: VASCULAR BIOLOGY, ADVANCED LIPID METABOLISM AND LIPOPROTEIN BIOCHEMISTRY**

### **A. Plaque Vulnerability**

- a. Pathology of Atherosclerosis
- b. Progression to Type I to Type IV Lesions
- c. Characteristics of Vulnerable Plaque
  - i. Lipid Core
  - ii. Fibrous Cap
  - iii. Vaso Vasorum
- d. Imaging of the Vulnerable Plaque
  - iv. IVUS
  - v. MRI
  - vi. Carotid B-mode Ultrasound – intima media thickness (IMT)
  - vii. Multiple Slice CT
  - viii. EBCT
- e. Predictors of Plaque Rupture

## **B. Transplant Atherosclerosis**

## **C. Thrombosis, Coagulation, and Rheology**

- a. Genetic Causes of Hypercoagulability
  - i. Factor V (Leiden) Mutation
  - ii. Hyperhomocysteinemia
  - iii. Protein C and S Deficiency
  - iv. Anti-thrombin III Deficiency
- b. Coagulation Cascade
- c. Platelet Aggregation and Antiplatelet Therapy
- d. Drug Induced Causes of Hypercoagulation
- e. Lp(a) and Atherosclerosis

## **D. Endothelial Progenitor Cells and Atherosclerosis**

## **E. Lipid and Lipoprotein Biochemistry**

- a. Cholesterol and Bile Metabolism
  - i. Overview of cholesterol synthetic pathway
  - ii. Focus on squalene synthase
  - iii. Side products of cholesterol synthesis, i.e., ubiquinone and prenylated proteins.
  - iv. Lanosterol as a marker of cholesterol synthesis.
  - v. Regulation of cholesterol metabolism
  - vi. Proteolytic regulation of HMG-CoA reductase
  - vii. Utilization of cholesterol
  - viii. Regulation of cellular sterol content
  - ix. Bile acid synthesis
  - x. Clinical significance of bile acid
- b. Fatty Acid and Triglyceride Metabolism
  - i. Fatty acid synthesis
  - ii. Hepatic-peripheral fatty acid cycling
- c. Nuclear Receptors and Gene Regulation
  - i. LXR
  - ii. FXR

- iii. HNF-alpha
- iv. PPARs, alpha, beta (delta) and gamma
- v. SREBP-1a, SREBP-1c, SREBP-2
- d. HDL Metabolism (RCT)
  - i. Chylomicrons in RCT
  - ii. Role of the intestine in cholesterol transport
  - iii. Cholesterol efflux from cells: ABC transporters
  - iv. Biliary cholesterol and RCT
  - v. Cholesterol Esterification by LCAT
  - vi. Transport to the liver (HDL to SRB1)
  - vii. HDL transport via CETP to ApoB (100 and 48) then to hepatic LDL receptor
  - viii. Hepatic control of biliary cholesterol excretion
  - ix. Elimination of acids and neutral fecal sterols
  - x. Disposition of reabsorbed biliary cholesterol and enterohepatic recycling
  - xi. Free cholesterol via NPC1L1 and bile acids via IBAT
- e. Evolving Targets of Therapy
  - i. HMR74A (niacin receptor)
  - ii. DP1, DP2
  - iii. HSD-1
  - iv. ANGPTL-4 (angiopoetic-like protein-4)
  - v. LXR
  - vi. FXR
  - vii. DGAT-1, DGAT-2
  - viii. PCKS-9
  - ix. ApoA1 mimetics
  - x. Squalene synthase inhibition
  - xi. RXR