University of Minnesota Lab Medicine and Pathology

Clinical Chemistry Rotation

Location:	VA Medical Center & University of Minnesota Medical Center
Duration:	Two months (2 weeks at VAMC; 6 weeks at UMMC)
Rotation Directors:	Jasbir Singh, PhD (office: 612-467-2499) Amy Karger, MD, PhD – (office: 612-624-2150, pager 612-899-5614)
Other Faculty:	Danni Li, PhD (office: 612-626-0299; cell: 612-499-0751), Anthony Killeen, MD,PhD (office: 612-625-5443), Joseph Rudolf, PhD (office: 612-626-2607), (Amy Saenger, PhD (office: 612-626-2607), Jesse Seegmiller, PhD (office: 612-625-6198)

General Description:
Residency training in clinical chemistry prepares an individual to provide services as a laboratory director at a community hospital or tertiary care center. After the rotation, the resident will be knowledgeable and experienced with analytical techniques and instrumentation used in clinical laboratories, the use and interpretation of laboratory tests in the diagnosis of disease, and therapeutic drug monitoring and toxicology. The resident will also receive an introduction to laboratory management principles.

Goals and Objectives:

VA chemistry topics:

- Introduction to Clinical Chemistry Analyzers and Analytical Techniques
    a) Be familiar with the automated random-access analyzers available for clinical laboratories
    b) Understand the measurement principles utilized on these analyzers, including:
        1. Spectrophotometry
        2. Fluorescence
        3. Ion-selective electrodes
        4. Nephelometry
        5. Turbidimetry
        6. Electrochemical methods
- Lab Automation and the Process of Selecting and Validating Clinical Chemistry Instrumentation
    a) Understand the principles of laboratory robotics and automation strategies
    b) Understand the factors that are involved in selecting clinical chemistry instrumentation, including:
        1. Test menus
        2. Finances: whether to lease, purchase, or obtain “free” for reagent costs
        3. Analytical methods used
        4. Quality of results
        5. Anticipated test volumes
    c) Understand the basic process for validating a new clinical chemistry instrument, including:
        1. Determination of within-run and total imprecision
        2. Calibration verification
        3. Comparison data between the old and new analyzers
        4. Reference range verification
- Therapeutic drug monitoring and toxicology
    a) List five reasons for performing drug analysis
    b) Know the definition and clinical utility of the following pharmacokinetic terms:
        1. Volume of distribution
        2. Half-life
        3. Clearance
        4. Loading dose
        5. Steady state
        6. Bioavailability

7. Therapeutic concentration
8. Peak
9. Trough

c) Know the principles that are involved in the measurement of therapeutic drugs by:
   1. Fluorescent polarization immunoassays (FPIA)
   2. Enzyme multiplied immunoassays (EMIT)
   3. Cloned enzyme donor immunoassay (CEDIA)
   4. Kinetic interaction of microparticles in solution (KIMS)
   5. High performance liquid chromatography (HPLC)
   6. Gas chromatography (GC) and GCMS
   7. HPLC with tandem mass spectrometry.

d) Know the advantages and disadvantages of measuring drug concentrations by immunoassay techniques compared to those that use HPLC or GC

- Basic concepts of Quality Control in the Clinical Lab
  a) Understand internal quality control programs
     1. What is the method precision?
     2. How are "action" and "warning" defined?
     3. How large is the analytical imprecision compared to the reference range?
     4. Would a more precise analytical method be useful clinically?
     5. Impact of Matrix effects on quality control
  b) Be familiar with external quality control programs (proficiency testing)
  c) Understand the difference between calibrators and controls
  d) Understand the basic principles of assay calibration and the need for calibration verification
  e) Be familiar with the Westgard Rules for QC

U of M chemistry topics:

Goals and objectives adapted from Smith BR et al, Curriculum Content and Evaluation of Resident Competency in Clinical Pathology (Laboratory Medicine): A Proposal. Clin Chem52:6 (2006), 917-949.

1. Assessment of pulmonary function – blood gases and oxygen saturation
   a. Understand the principles of partial pressure of gases and the need for an O_2 carrier
   b. Be able to describe the alveolar-arterial O_2 gradient and anion gap
   c. Know the pathophysiology of ketoacidosis and lactic acidosis
   d. Understand the significance of P_{50}, O_2 content, O_2 capacity, and O_2 saturation and P_{O2}
   e. Be able to describe the hemoglobin-oxygen dissociation curve and factors that affect the curve and P_{50}
   f. Understand the principles of integrated blood gas, electrolytes and CO-oximetry systems
2. Acid-base chemistry, electrolytes and relevant disorders
   a. Define the Henderson-Hasselbach equation
   b. Understand the physiologic buffer systems and the role of respiratory and renal compensation
   c. Understand the categories of clinical disorders of acid-base balance, such as metabolic acidosis or alkalosis, respiratory acidosis or alkalosis, or mixed disorders
   d. Know the differential diagnosis of common electrolyte disorders
3. Assessment of renal function
   a. Know the basic physiology of renal function
   b. Understand the basic categories of renal diseases and be families with the National Kidney Foundation practice guidelines for these conditions
   c. Know the laboratory analytical methods for the assessment of renal function (creatinine, BUN, GFR) and proteinuria
   d. Understand the equations used to estimate GFR (i.e. MDRD, CKD-EPI, Cockcroft-Gault)
   e. Understand the concept of creatinine clearance, how it is used to estimate GFR, and the various methods employed to measure it
   f. Understand the renal handling of electrolytes and key metabolites and the interpretation of urinary electrolyte measurements
   g. Understand the definition of osmolality, calculation of osmolal gap, and the principle of the osmometer

h. Understand the common pitfalls and sources of error during estimation of the osmolal gap, e.g. hyperproteinemia, hyperlipidemia, hypermagnesemia
i. Understand the differential diagnosis of unexplained, increased osmolal gap, including alcohol or glycol ingestion, alcoholic or diabetic ketosis or ketoacidosis, and osmotherapy (e.g. mannitol or glycerol administration), etc.
j. Understand the principles of fluid balance

4. Cardiac biomarkers for the assessment of coronary artery disease
    a. Know the current definition of myocardial infarction by the European Society of Cardiology/American College of Cardiology guidelines and the New York Heart Association classifications and understand the interaction of diagnostic modalities in its definition (electrocardiogram, laboratory testing, and imaging)
    b. Know the diagnostic and prognostic significance as well as the limitations of current coronary artery disease biomarkers [troponins I and T, creatinine kinase (CK-MB index and isoforms), and myoglobin]
    c. Know the pathophysiology and evaluation of congestive heart failure. Understand the markers of congestive heart failure [B-type natriuretic peptide (BNP) and N-terminal fragment of the BNP prohormone (NTproBNP)] and their biological and technical limitations
5. Assessment of liver and biliary tract status
    a. Understand the dynamics and mechanisms of liver enzyme release and the clinical utility of measuring hepatic enzymes (e.g., aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, alkaline phosphatase, and lactate dehydrogenase).
    b. Know the biochemical assessment of liver function by nonenzyme analytes such as albumin, ammonia, bile acids, bilirubin, urea nitrogen, cholesterol, total protein, and triglycerides.
    c. Understand bilirubin metabolism, fractionation of bilirubin (conjugated, unconjugated, delta-bilirubin, direct vs indirect) and unique aspects of neonatal bilirubin
    d. Understand the conditions and genetic defects that affect bilirubin metabolism, transport and clearance (e.g., Gilbert disease and Dubin–Johnson syndrome)
6. Assessment of thyroid function
    a. Understand the structure, biosynthesis, secretion, and metabolism of thyroid hormones [thyroxine (T4), triiodothyronine (T3), and reverse T3 (rT3)]
    b. Know thyroid physiology and control of thyroid function [thyrotropin- releasing hormone (TRH) and thyrotropin (TSH)]
    c. Know the common causes of hypothyroidism and hyperthyroidism
    d. Know the laboratory tests for evaluation of thyroid disorders and be able to interpret these analytes in their clinical context with an appreciation for the euthyroid sick state.
    e. Be familiar with current analytical methodologies for thyroid testing (TSH methods: 1^{st}, 2^{nd}, and 3^{rd} generation assays; isotopic and nonisotopic methods; T4; free T3 methods; T-uptake methods; TSH suppression and stimulation tests)
7. Assessment of pituitary function
    a. Understand the physiological action, biochemistry, and regulation of anterior pituitary hormones [adrenocorticotropic hormone (ACTH), growth hormone (GH), prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH)] and of posterior pituitary hormones [antidiuretic hormone (ADH) and oxytocin]
    b. Understand endocrine tests of hypothalamic-pituitary function (cosyntropin test/rapid ACTH stimulation test, insulin hypoglycemia test, metyrapone test, levodopa test, arginine infusion test, glucose-GH suppression test, TRH test, gonadotropin-releasing hormone (GnRH) test, clomiphene test, corticotropin-releasing hormone (CRH) test, gonadotropin-releasing hormone test, water deprivation test, saline infusion test, and water loading test)
    c. Understand the pathophysiology of disorders of the pituitary
8. Assessment of adrenal function
    a. Understand the physiological action, biochemistry, biosynthesis, chemical structure, and metabolism of glucocorticoids and mineralocorticoids.
    b. Understand the physiological regulation of the reninangiotensin-aldosterone system.
    c. Understand clinical conditions associated with excess and deficiency of adrenal cortex hormones.

    d. Understand testing of the functional status of the adrenal cortex [basal values vs stimulation tests and suppression tests, circadian rhythm of corticosteroids, morning ACTH, cortisol (urinary, random, and free), rapid ACTH cortisol stimulation test, multiday ACTH stimulation, metyrapone stimulation, CRH stimulation and quantitative serum and urinary steroid hormone panels]
    e. Understand the synthesis and metabolism of biogenic amines, including catecholamines and serotonin
    f. Be familiar with the strengths and weaknesses of tests available for evaluation of disorders of the adrenal medulla, such as pheochromocytoma and neuroblastoma
9. Assessment of reproductive function, pregnancy and prenatal testing
    a. Understand the role of sex hormones in reproduction and the evaluation of pregnancy and reproductive dysfunction, such as menstrual disorders and infertility
    b. Understand the importance of demographic data and biochemical assessment in prenatal testing for fetal defects
10. Assessment of gastric, pancreatic and intestinal function
    a. Understand the clinical manifestations of gastric, pancreatic, and intestinal disease and diagnostic methodologies such as the breath tests for *Helicobacter pylori*, fecal occult blood, lipase, and amylase (e.g., fractionation of amylase; pancreatic vs salivary and amylase/creatinine clearance ratio).
    b. Appreciate the role of gastrointestinal hormones and enzymes in digestion and the evaluation of malabsorption and diarrheal syndromes.
11. Assessment of glucose and evaluation of diabetes mellitus
    a. Understand the metabolism of carbohydrates (insulin, C-peptide, and other regulatory hormones) and be familiar with the American Diabetes Association (ADA) definitions of impaired fasting glucose, impaired glucose tolerance, type 1 and type 2 diabetes mellitus, criteria for diabetic ketoacidosis and hyperosmolar hyperglycemic state, as well as gestational diabetes. Understand the underlying pathophysiology of different forms of diabetes.
    b. Understand the diagnosis and laboratory assessment of diabetes (blood glucose, oral glucose tolerance test, hemoglobin A1c, fructosamine, and urinary microalbumin) and its complications.
    c. Understand the diagnosis and evaluation of hypoglycemia.
12. Assessment of mineral and bone metabolism
    a. Understand the biochemistry and physiology of calcium, phosphate, and magnesium
    b. Know the hormones that regulate mineral metabolism [parathyroid hormone (PTH), calcitonin, and vitamin D] as well as parathyroid hormone-related protein (PTHrP)
    c. Understand various PTH assays, including biointact PTH and intraoperative PTH
    d. Know the pathophysiology of metabolic bone diseases such as osteoporosis, osteomalacia, and Paget disease
13. Assessment of porphyrins and disorders of porphyrin metabolism
    a. Understand the biochemistry of heme and porphyrins
    b. Understand the porphyrias and be able to consult on the selection and interpretation of both screening and diagnostic tests for each disorder
14. Tumor biomarkers
    a. Be familiar with the definition, classification, biochemistry, and distribution of tumor markers, both protein and carbohydrate, including, but not limited to, prostate-specific antigen, calcitonin, human chorionic gonadotropin, alpha-fetoprotein, carcinoembryonic antigen, CA 15-3, CA 125, and CA 19-9
    b. Know the limitations of laboratory assessment of various tumor markers and the factors affecting the results of different analytical procedures
    c. Understand the conceptual basis of assays used to screen for malignancy, including Bayes theorem
15. Trace element assessment
    a. Understand the biochemistry, physiology, and metabolismof trace elements (iron, magnesium, zinc, copper, selenium, cobalt, and fluoride). Know the biochemistry and clinical significance of metal-binding proteins such as transferrin, ferritin, and ceruloplasmin

    b. Know the clinical assessments of trace elements (serum iron, iron-binding capacity, transferrin, transferrin saturation, serum ferritin, zinc protoporphyrin, and serum ceruloplasmin)
16. Vitamin assessment
    a. Know the definition and classification of vitamins: fat-soluble vitamins (A, D, E, and K) and water-soluble vitamins [B1, B2, B6, B12 (cobalamin), C, niacin, nicotinamide, folic acid, biotin, and pantothenic acid]
    b. Understand the clinical disorders associated with the deficiency as well as toxicity of vitamins
17. Cholesterol and lipid assessment
    a. Understand the chemical structures, biosynthesis, classification, function, and metabolism of lipids and lipoproteins.
    b. Understand the Fredrickson classification and the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP IV) classification of hyperlipidemia
    c. Understand the pathophysiology of lipid disorders
    d. Know the principles of analytical techniques for laboratory assessment of lipids
18. Serum and fluid protein and amino acid assessment
    a. Understand the principles of protein analysis in body fluids (e.g., Kjeldahl and Biuret methods, refractometry, and qualitative dipstick)
    b. Know the principles of serum, urine, and cerebrospinal fluid (CSF) protein electrophoresis
    c. Recognize key patterns of dysproteinemias and monoclonal gammopathies
    d. Understand approaches for distinguishing transudates vs exudates in fluids
    e. Know the analytical methods involved in genetic and acquired aminoacidurias and the current guidelines for screening neonates for these disorders
19. Clinical enzyme kinetics
    a. Understand the principles of enzyme kinetics (e.g., Michaelis–Menten equation, concepts of *K*m, *V*max, and zero-order and first-order kinetics) and clinical enzymology, including isoenzymes, isoforms, and tissue distribution
    b. Be familiar with the principles of analytical enzymology and know the concepts of activity vs mass assays (e.g., CK vs CK-MB assays)
20. Pediatric biochemistry
    a. Understand the difference and unique aspects of pediatric and neonatal chemistry, including reference ranges
21. Pharmacokinetics
    a. Understand the concepts of drug absorption, bioavailability, volume of distribution, and distribution phases (multicompartment models) and be able to predict peak drug levels
    b. Understand the differences between first- and zero order kinetics of drug metabolism/elimination
    c. Understand the concepts of drug clearance, half-life, and the exponential rate constant. Be able to calculate steady-state drug levels and estimate peak and trough drug levels throughout a dosing cycle
    d. Understand the origin and consequences of nonlinear or zero-order pharmacokinetics on drug pharmacokinetics
    e. Understand the differences between measurement of total, free, and protein-bound drug levels and be able to assess the consequences of altered protein binding on pharmacokinetics and therapeutic drug monitoring
22. Drug metabolism
    a. Understand the differences between phase I and phase II drug metabolism reactions
    b. Appreciate the various consequences of competing metabolic pathways to modulate both the efficacy and toxicity of administered medications
    c. Appreciate the frequent interindividual variability of drug-metabolizing enzymes and its impact on the variability of drug response
23. Therapeutic drug monitoring of specific drug classes

a. Understand the principles and practice of therapeutic drug monitoring of antidepressants, mood stabilizers, and antipsychotics; anticonvulsants; cardioactive drugs; bronchodilators; antibiotics; and immunosuppressants
b. Understand the relative significance of peak and trough levels for monitoring of these drug classes

24. Laboratory evaluation and management of overdosed or poisoned patients
    a. Be familiar with the National Academy of Clinical Biochemistry guidelines for Emergency Toxicology
    b. Understand the important differences between urine and blood (including serum and plasma) for monitoring and detection of drugs/xenobiotics
    c. Understand how to design and implement standardized STAT panels of laboratory tests for evaluation of overdosed/poisoned patients
    d. Understand the limitations of drug "screening" protocols and be able to consult on the design of more extensive drug-testing protocols to supplement the standard STAT panels
25. Laboratory evaluation of drugs of abuse
    a. Understand the generic methodology of the routine immunoassays for drugs-of-abuse testing
    b. Be familiar with the major drugs of abuse and their clinical manifestations
    c. Know the common methods for adulteration of urine and the techniques available in the laboratory to detect them

The learning objectives below reference the corresponding ACGME core competencies: Patient Care (PC), Medical Knowledge (MK), Professionalism (Prof), Communication Skills (CS), Practice Based Learning and Improvement (PBLI), and Systems-Based Practice (SBP).

- Analyzes, appraises, formulates, generates and effectively reports consultation on clinical chemistry cases (PC1)
- Demonstrates attitudes, knowledge, and practices that incorporate evidence-based medicine and promote life-long learning (MK1)
- Demonstrates attitudes, knowledge, and practices that contribute to patient safety (SBP1)
- Explains, recognizes, summarizes, and is able to apply quality improvement, risk management and safety issues (SBP4)
- Explains, recognizes, summarizes and is able to apply test utilization (SBP5)
- Displays attitudes, knowledge, and practices that permit improvement of patient care from study of errors and discrepancies (PBLI1)
- Analyzes and appraise pertinent literature, applies scientific method to identify and interpret evidence-based medicine and apply it clinically (PBLI2)
- Demonstrates honesty, integrity, ethical behavior, responsibility and follow-through on tasks (PROF2/PROF3)
- Displays attitudes, knowledge, and practices that promote safe patient care through team interactions and leadership skills within the laboratory and through interdisciplinary team interactions (ICS1/ICS2)

Assigned Reading:

- Required textbook: Contemporary Practice in Clinical Chemistry (2 copies in resident room). Select chapters will be assigned for rounds and chapters relevant to lectures should be reviewed prior to each lecture.

Optional Reading:

- For more detailed information on clinical chemistry topics, the Tietz Textbook of Clinical Chemistry and Molecular Diagnostics is the primary reference book for chemistry topics.

Call Duties: While on the clinical chemistry rotation, residents will be expected to share pager call duties with the fellows and other resident(s) on service. Additionally while on call the resident will address emails related to patient-testing issues that are sent by the faculty on the service. If guidance is needed responding to a call, the resident should first contact one of the fellows with questions, and then contact Dr. Danni Li or Dr. Amy Karger with questions. Calls should be documented using the Chemistry Call Documentation Sheet. Residents should be prepared to present these cases at the weekly chemistry call rounds held every Thursday.

During the rotation, the trainee is expected to join the following conferences:

- Clinical pathology conference, noon – 1 pm Tuesdays
- Laboratory Medicine Grand Rounds, 8 – 9 am Wednesdays
- Resident didactics, 9:15 – 10:15 am Wednesdays
- Clinical chemistry call rounds, 11:15 am – 12:15 pm Thursdays, Mayo 760-5
    a. Call rounds are attended by residents, fellows and faculty
    b. We review any pager or email "calls" from the week, so if a resident was on call they will be expected to lead discussion on the calls
    c. Residents and fellows will be expected to discuss any lab-related projects they are working on
    d. Lastly, each week at call rounds residents and fellows will be assigned a chapter to read in the textbook, will review case reports published in the Clinical Chemistry journal, review news articles on clinical chemistry topics, or do a journal club
        i. The schedule for call rounds which lists the reading assignment for the week is located on the LabMed server, in the folders /Clinical Chemistry/Chemistry Rotations/Chemistry Rounds/
        ii. Fellows will also email a weekly agenda for call rounds the day prior
        iii. If the chapter assigned for call rounds is a disease-based topic (such as thyroid) you are expected to look up a case (with the fellows' assistance) and present a case of a patient with a disorder relevant to the chapter. For methodological chapters, cases are not required.
- Acute Care East meeting, 9 – 10 am Thursdays
    a. Residents will be expected to meet with Dr. Danni Li and the fellows in the acute care lab East (back corner of the lab) every Thursday morning
    b. This meeting occurs with lab supervisors and is representative of the type of meeting laboratory directors have with laboratory staff to review operational and testing concerns
- Medical Advisory Committee (MAC) meetings, TBD
    a. There will be once monthly MAC meetings which involve laboratory supervisors from both West and East Bank, fellows, and Drs. Danni Li and Amy Karger
    b. These meetings are utilized to discuss campus-wide laboratory testing issues
- Quality meetings, TBD
    a. Quality meetings are held once monthly, typically on the third Thursday of the month at 1:30 pm
    b. These meetings provide a general overview of the quality metrics monitored for laboratory performance, as well as an update on quality improvement projects ongoing in the laboratories
- M&M conference, noon – 1 pm Fridays
    a. Residents are required to attend the weekly M&M conference put on by the Department of Internal Medicine, to gain exposure to the impact of laboratory testing on complex cases
    b. The location of the conference is published here: http://www.dom.umn.edu/department-of-medicine-weekly-conferences/
    c. Pizza and drinks are provided for lunch

Other Requirements:

- During the rotation residents will be required to attend protein electrophoresis sign-out. Sign-out can occur anytime between noon – 4 pm. Sign-out occurs in Mayo L260. The protein lab will be given the resident's pager number at the start of the rotation and will

page when sign-outs are ready. When the lab pages the resident, the resident should call back right away so the lab can inform the resident whether to come now or later, depending on faculty availability. If a resident is in a lecture or on a bench rotation, the resident should let them know that they are not able to come by that day for protein sign-out, as lectures and lab sessions take precedence over protein sign-out.

- CP case logs should be emailed to the rotation director throughout the rotation to meet program requirements. Dr. Karger will review all cases during the rotations and email feedback to residents. Resident is responsible to upload to the case log repository (available through the resident intranet).
- To meet pathology milestone requirements laid out by the ACGME and ABP, residents will be required to complete a quality improvement project while on their clinical chemistry rotation. Projects will be assigned at the beginning of the rotation and will be small projects that can be completed during the 6 week rotation.

Assessment methods:

Resident performance on this rotation will be assessed by:

- Pre- and post-test: Residents will take a pre- and post-test during the rotation at the University, at the beginning and end of the rotation. The main purpose of this exam is to assess whether faculty are effectively teaching residents the material.
- Residents will be evaluated on performance of daily activities (described previously), handling of chemistry calls, participation in required meetings, conferences and lectures, and on presentations to the staff on assigned cases. Residents will receive feedback as needed throughout the rotation. The resident will also receive in-person feedback from Dr. Karger, the rotation director, after review of the post-test is complete on the last day of the rotation.