PEDIATRIC AND MATERNAL-FETAL DIVISION NEWS
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AACC Better health through laboratory medicine.

FROM THE MIND OF THE CHAIR

I hope everyone is enjoying summer and looking forward to the AACC Annual meeting beginning on July 23rd. The PMF Division is also co-hosting a Mixer with the Health Equity and Access, History, and Informatics Divisions on Sunday night. Join us for food and drinks and networking with your colleagues. Congratulations to our abstract award winners and the Outstanding Contribution to Pediatric and Maternal-Fetal Clinical Chemistry award winner who are announced in this newsletter. They will also be recognized at the mixer.

In this issue Rebecca Wilson addresses L in The ABC's of Pediatric Laboratory Medicine series, penning an article titled L is for Lipids. Excerpts from the Literature discusses the challenges associated with high-sensitivity cardiac troponin authored by Emily Garnett from Texas Children's. Also included is an extensive list of sessions that might be of interest to our members. Thank you to the newsletter team for making it easy to plan out our annual meeting schedule.

This year's annual scientific meeting marks the 75th anniversary of our organization. As you know, AACC is rebranding to be more inclusive of all who work in or with the clinical lab. This change also reflects who the organization already serves. The changes to ADLM also allows us to adapt to reflect a more inclusive, collaborative, and influential future of the field. This is an exciting time for our organization. I urge you to embrace this change and continue to actively participate within our division.

As I near the end of my first year and I am honored to work with an intelligent and active group of members. I look forward to the upcoming year with great anticipation.

See you in Anaheim!

Sincerely,

Stanley F Lo
Chair, AACC PMF Division

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THE ABC'S OF PEDIATRIC LABORATORY MEDICINE:

L is for lipids: A brief review

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Background

Cardiovascular diseases, including heart disease, stroke, and related vascular deaths, are leading causes of morbidity and mortality in the United States. Recent research has shown that many cardiovascular deaths in adulthood have their origins during childhood. Abnormal lipid levels in children and adolescents are prevalent, with approximately 20 percent of individuals aged 6 to 19 years having abnormal lipid values [1]. Lipid testing in pediatric populations is a crucial diagnostic tool used to assess the lipid profile of young individuals [2]. Lipids, such as cholesterol and triglycerides, play essential roles in various physiological processes. However, imbalances in lipid levels can contribute to the development of cardiovascular diseases and other health complications later in life [3]. Early detection and management of abnormal lipid levels are therefore essential for preventing long-term health consequences.

Lipid testing plays a critical role in the evaluation and management of pediatric patients with dyslipidemias, disorders affecting lipoproteins' metabolism. Dyslipidemias encompasses a range of conditions that can lead to abnormalities in lipid levels, including elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), or triglycerides, as well as decreased levels of high-density lipoprotein cholesterol (HDL-C).

One notable example of inherited dyslipidemia is familial hypercholesterolemia, which highlights the importance of monitoring lipid levels in childhood. High LDL cholesterol levels characterize familial hypercholesterolemia and serve as a compelling illustration of the link between childhood lipid levels and subsequent cardiovascular events [3]. This condition is often caused by gene mutations associated with LDL receptor function or other proteins involved in LDL metabolism [3].

Heterozygous familial hypercholesterolemia is relatively common, occurring in approximately 1 in 500 individuals [3]. It is essential to diagnose this condition early in life because untreated affected males have a significantly increased risk of developing cardiovascular disease by the age of 50 [3]. By identifying and managing elevated lipid levels in pediatric patients with heterozygous familial hypercholesterolemia, healthcare providers can intervene early to mitigate the risk of cardiovascular complications later in life.

On the other hand, homozygous familial hypercholesterolemia, although rare, is a more severe condition that can lead to clinical cardiovascular disease before adulthood. Individuals with this condition have extremely high levels of LDL cholesterol due to the presence of two abnormal copies of the LDL receptor gene or other related genes. Without appropriate intervention, homozygous familial hypercholesterolemia can result in the early onset of cardiovascular disease, underscoring the significance of early identification and aggressive management strategies.

Laboratory Testing for Lipids

Several types of assays are used to measure lipids in pediatric populations, allowing for the quantification of various components of the lipid profile. The methods employed can be categorized as enzymatic, non-enzymatic, or

homogenous. Enzymatic assays utilize cholesterol oxidase, cholesterol esterase, or a combination of both, followed by a Trinder's reaction. The resulting reaction is quantified spectrophotometrically to measure total cholesterol, HDL-C, LDL-C, and triglycerides. Non-enzymatic assays rely on chemical reactions that produce colorimetric or fluorometric signals. The Liebermann-Burchard reaction and ferric chloride reaction are commonly used in non-enzymatic assays. Another technique, ultracentrifugation, can be employed to isolate and separate lipoproteins based on their density before quantification by spectrophotometry. Although considered the gold standard, ultracentrifugation is less commonly used in routine clinical practice due to its complexity and time-consuming nature.

Estimation of LDL-C

Accurate measurement of LDL cholesterol is crucial for effective patient management and appropriate adjustment of statin therapies. Traditionally, the Friedewald equation, introduced in 1972, has been widely used for the calculation of LDL cholesterol. However, this equation has limitations, particularly in patients with high triglyceride concentrations, as it may not consistently provide accurate estimations of LDL cholesterol at low concentrations [5].

To address this issue, a new equation was developed by Sampson et al. in 2020. This equation was formulated based on residual samples from patients tested at the NIH Clinical Center and has demonstrated improved accuracy and reliability in estimating LDL cholesterol levels, particularly in large cohort pediatric studies [12]. In comparison, the Friedewald equation significantly underestimated LDL cholesterol levels across all age groups, especially in patients with elevated triglyceride concentrations (with an average TG of 90.3 ± 77.9 mg/dL among all 2,605 patients) [6].

In another study involving 3,908 pediatric patients under 18 years of age, the accuracy of LDL cholesterol estimation was evaluated using various formulas, including the Friedewald, Martin/Hopkins, extended Martin-Hopkins, and Sampson's equations. The study found that the Friedewald formula yielded the highest degrees of underestimation, while the extended Martin-Hopkins equation provided more reliable results in estimating LDL cholesterol levels compared to other equations, including Sampson's formula [7].

Recommended Guidelines

Optimal lipid levels are 1 of 7 critical factors that define ideal cardiovascular health during childhood according to the American Heart Association [11]. Universal screening of pediatric patients has been widely recommended by several national and international health organizations. In 2011, the National Heart, Lung, and Blood Institute (NHLBI) expert panel published guidelines for cardiovascular health and CVD risk reduction in youth by strongly recommending universal screening [11]. The American Academy of Pediatrics (AAP) in tandem with these guidelines recommends universal lipid screening between the ages of 9 and 11, followed by a second screening between 17 and 21 years [4]. Earlier testing is recommended if there are risk factors present. For high-risk patients such as children with a family history of early-onset cardiovascular diseases, obesity, or other risk factors should undergo targeted screening starting at 2 years old [4,11]. Recommended values for total cholesterol, non-HDL, LDL, HDL, and triglycerides can be found in Table 1 outlining acceptable, borderline, and abnormal ranges.

Lipoprotein (a): An additional marker with potential

Lp(a) has emerged as an important risk factor in determining statin treatment thresholds for children with familial hypercholesterolemia [9]. It is particularly significant because it has been shown to contribute significantly to the risk of atherosclerotic cardiovascular disease (ASCVD) in adults with familial hypercholesterolemia. The recent study by Raitakari et al. reinforces the association between Lp(a) and increased ASCVD risk in adulthood, highlighting that it acts

independently and additively with LDL cholesterol[8]. Children with elevated levels of both Lp(a) (>30 mg/dL) and LDL cholesterol (>130 mg/dL) face more than four times the risk of premature ASCVD compared to those with normal levels [8].

Table 1. Interpretation of lipid results in pediatric populations

	Acceptable	Borderline	Abnormal
Total cholesterol	<170	170-199	≥ 200
Non-HDL	< 120	120-144	≥ 145
LDL	<110	110-129	≥ 130
HDL	>45	40-45	< 40
Triglycerides (age 0 to 9 years)	<75	75-99	≥ 100
Triglycerides (age 10-19 years)	<90	90-129	≥ 130

These findings support including Lp(a) screening alongside universal lipid screening recommendations in childhood. Unlike other cardiovascular risk factors that may vary over time, the stability of Lp(a) levels due to genetic determination means that screening would only need to occur once [8]. This would enable more precise risk assessment and earlier and more aggressive management of other cardiovascular risk factors. Moreover, elevated Lp(a) levels should be considered an additional risk factor in children and can help guide decisions regarding statin initiation for hypercholesterolemia [9].

The potential impact of Lp(a)-lowering therapies in childhood, as they become available, on reducing cardiovascular risk in adulthood is an important question that requires further evaluation. Implementing systematic Lp(a) screening strategies early in life may also open avenues for reverse cascade screening, addressing adult testing gaps. Overall, incorporating Lp(a) screening into childhood assessments offers opportunities for improved risk stratification, earlier intervention, and enhanced management of cardiovascular risk factors, ultimately aiming to reduce the burden of ASCVD later in life [10].

Conclusion

By conducting lipid testing in pediatric patients, healthcare professionals can identify dyslipidemias, including familial hypercholesterolemia, at an early stage. Timely detection allows for targeted interventions such as lifestyle modifications, dietary changes, and, in some cases, pharmacological treatment to optimize lipid levels and reduce the risk of cardiovascular complications in the long term. Moreover, lipid testing in pediatric populations provides an opportunity for early education and counseling on heart-healthy lifestyles, emphasizing the importance of maintaining healthy lipid levels from an early age to promote cardiovascular health throughout life.

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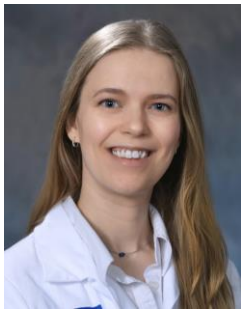
Excerpts from the Literature



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Assistant Professor of Pathology and Immunology, Baylor College of Medicine

High-sensitivity cardiac troponin in pediatrics: where are we now?

High-sensitivity cardiac troponin (hs-cTn) is now a widely used cardiac biomarker in adult practice. The 2021 American College of Cardiology/American Heart Association Guidelines for the Evaluation and Diagnosis of Acute Chest Pain, in fact, specifically cite hs-cTn tests as the preferred biomarker for establishing a diagnosis of acute myocardial infarction in adults, as well as a biomarker to categorize patients with suspected acute coronary syndrome into low, intermediate, and high-risk groups (1). Yet, appropriate interpretation of hs-cTn measurements hinges on the availability of appropriate 99th percentile reference limits – which can be challenging to generate given the large sample sizes required. In pediatrics, this is an even more difficult issue, and one that is only compounded by the rapid physiological changes that occur during infancy and childhood. This often necessitates extensively partitioned reference intervals, further increasing the required sample size.

Cardiac troponin (cTn) is one such analyte that is known to vary substantially by age. Concentrations of cTn have long been understood to be dynamic in early childhood, which has been attributed to multiple factors, including changing rates of cardiomyocyte renewal, expression of fetal cTn in skeletal muscle, transient hypoxia at birth, or immature renal function in neonates (2). The absence of appropriate 99th percentile reference limits for pediatrics has been a major historical barrier to interpretation of hs-cTn results and has precluded the establishment of clinical guidelines for the use of hs-cTn in this patient population (3).

A recent publication from the CALIPER initiative represents a step toward solving this problem, highlighting newly established reference intervals for hs-cTnI and NT-proBNP in a pediatric cohort. The authors report a 99th percentile upper reference limit of 55.8 ng/L for the 0-6 month age group and 5.5 ng/L for the 6 month-19 years age group, which agrees with earlier studies demonstrating that cTn concentrations are high in neonates and decline over infancy and childhood (4). While this is a significant advance, the authors highlight several

important limitations of their study: namely, the sample size for the 0-6 month age group is small (49 individuals), and the QC available for their assay did not extend to the low concentrations of hs-cTnI observed in children older than 1 year of age. The study also established reference intervals for a single assay and instrument, and there are multiple FDA-approved hs-cTn assays that are not equivalent to one another (3).

It is important to note, likewise, that establishment of reference intervals for hs-cTn is only one aspect of how hs-cTn may be used clinically in pediatrics. A recent set of recommendations published in Clinical Chemistry made the following suggestions for use of hs-cTn in pediatrics: 1) to convene a consortium of experts to define the analytical and clinical data needed, 2) to define 99th percentile upper reference limits for all hs-cTn assays, age, and sex groups, 3) to conduct studies in specific clinical groups, such as congenital heart disease and patients at risk for myocarditis, 4) to use cardiac imaging to clarify clinically relevant increases in hs-cTn, and 5) to start a registry for longitudinal studies to establish the prognostic value of hs-cTn (3).

Currently, there is very little information on the clinical utility of hs-cTn in pediatrics, and no clinical practice guidelines exist (2). A recent retrospective study of hs-cTn in a pediatric cohort highlighted this issue: the authors did not observe a consistent approach by clinicians to ordering this test, nor a consistent type or level of follow-up after testing. The authors noted that different clinical scenarios observed in their patient population may have explained the variation in follow-up, such as different management in congenital heart disease and in sepsis (5). Indeed, while some studies show analogous findings in adult and pediatric populations with respect to risk of adverse cardiovascular events and hs-cTn levels, the most common pediatric cardiac diagnoses differ from diagnoses seen in the adult emergency department (3). Consequently, measuring hs-cTn for nonspecific chest pain in pediatric patients is not recommended (2), and further studies are needed to explore the clinical utility and prognostic value of hs-cTn for pediatric patients.

So where are we now with hs-cTn in pediatrics? The latest studies represent a leap forward for appropriate and informed clinical use, but much more work will be needed before we have clinical guidelines for pediatrics. In the meantime, consider the recommendation from our colleagues, published in Clinical Chemistry: that hs-cTn should be considered on an individual basis, and ordered when the results are likely actionable (3).

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2023 AACC ANNUAL SCIENTIFIC MEETING & CLINICAL LAB EXPO: PMF Sessions of Interest and Meeting Highlights

July 23-27, 2023

Sunday July 23rd

Opening Plenary:

Jeffrey I. Gordon, MD
11001 Developing Microbiome-Directed Therapeutics for Treating Childhood Undernutrition

PMF Division Mixer co-hosted with the Divisions of Health Equity & Access, History, and Informatics

8:00-9:30 PM Platinum 1, Anaheim Marriott. Awards will be presented during this time.

Monday July 24th

Roundtables:

42105 and 52205 Cystic Fibrosis: More Than Just Lung Function

42108 and 52208 Hemoglobin Fractionation by Capillary Electrophoresis: A Case-Based Laboratory Analysis of Hemoglobinopathies

42114 and 52214 Laboratory Best Practice in Ameliorating Risk of Diabetes Mellitus Postpartum

Plenary:

Atul Butte, MD, PhD
12001 Precisely Practicing Medicine from 700 Trillion Points of Data

Scientific Sessions:

32106 Interpretation of Pediatric Toxicology Results in the Assessment of Child Maltreatment

32109 Hype, Hope, or Already Here: The Status of Non-Invasive Prenatal Screening and Liquid Biopsies

32447 Cystic Fibrosis: Treatment, Diagnosis, and Laboratory Best Practices

12002 AACC Disruptive Technology Award Competition

Tuesday July 25th

Roundtables:

43124 and 53224 Revising Laboratory Practice to Meet the New American Academy of Pediatrics Guidelines for Management of Hyperbilirubinemia

43128 and 53228 Thyroid Disease in Pregnancy: How Much do We know?

Plenary:

Thea James, MD, MPH, MBA
13001 Choosing Equity in Healthcare: An Organizational Transformation

Scientific Sessions:

33106 A Guide to Interpreting Complex Urine, Umbilical Cord, Meconium, and Hair Toxicology Cases

Wednesday July 26th

Roundtables:

44110 and 54210 Establishment of Pediatric Reference Intervals

44124 and 54224 Newborn Screening and Follow-up for Metabolic Disorders

44126 and 54226 Pediatric Steroid Hormone Measurements by LC-MS/MS: A Clinical Diagnostic Lab Practice

Plenary:

Nanette Wenger, MD, MACC, MACP, FAHA
14001 Cardiovascular Disease in Women: Epidemiology, Awareness, Access, and Delivery of Equitable Health Care

Scientific Sessions:

34228 AACC Academy's Clinical Laboratorian and Clinician Conversations: In Vitro Fertilization and Ectopic Pregnancy

34109 Infectious Diseases Serology Potpourri: Diagnosis of Common Congenital and Not So Common Viral Hepatitis infections

Thursday July 27th

Plenary:

Mark Walters, MD
15001 Advances in Curative Therapies for Sickle Cell Disease

Scientific Sessions:

35105 Pediatric Lipid Screening: The Heart of the Matter

35107 Biochemical and Molecular Insights into Newborn Screening Disorders Both Old and New

PMF Division Awardees

Please help us congratulate the winners of this year's PMF Division Awards!

Best Abstract by a Student or Young Investigator:

Rogers Muldrow
Research and Development Scientist
Let's Get Checked
Title: Development and validation of an ICP-MS method to quantify lead in dried blood spots

Best Abstract:

Jennifer Powers Carson, PhD
Associate Professor of Medicine
Washington University School of Medicine
Title: Unusually Low Glycated Albumin Results Suggest Unexpected Interference in Study Samples from Pregnant Women

Outstanding Contributions to Pediatric Maternal-Fetal Laboratory Medicine:

Alison Woodworth, PhD, FAACC, DABCC
Clinical Director
Global Laboratory Services

PMF Division Executive Board:

Thank you to our division officers who will be completing their terms this month.

They are:

Past Chair
Angela Ferguson, PhD

Members At Large
Jane Dickerson, PhD
Van Leung-Pineda, PhD

Fellow Representative
Catherine Laaripuoh Omosule, PhD

Elections have not yet been completed for new officers.
Our remaining officers are:

Chair
Stanley Lo, PhD

Chair Elect:
Joe Wiencek, PhD

Members At Large
Stephen Roper, PhD
Sydney Webb Strickland PhD
TBD
TBD

Secretary:
Laura Smy, PhD

Treasurer:

Erin Schuler, PhD

Newsletter Editor
Sarah Wheeler, PhD

Newsletter Editorial Board
Emily Garnett, PhD
Stephen Roper, PhD

Fellow Representative: TBD