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Direct Oral Anticoagulant Therapy–Mechanisms and Monitoring

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Introduction

For decades, vitamin K antagonists (VKA) such as warfarin have been the mainstay for chronic anticoagulation. However, VKAs are characterized by numerous drug and dietary interactions, exhibit a narrow therapeutic index (defined by International Normalized Ratio), and require frequent laboratory testing and dose adjustments. Over the past decade, several direct-acting oral anticoagulants (DOACs) have emerged. In 2010, the direct thrombin inhibitor dabigatran received FDA approval for stroke prevention in atrial fibrillation, followed by FDA approval for several direct factor Xa inhibitors: rivaroxaban in 2011, apixaban in 2012, edoxaban in 2015, and betrixaban in 2017 (betrixaban was discontinued in 2020 and therefore is not discussed further in this review). DOACs offer similar or better efficacy and a safer risk profile compared to VKAs due to more favorable pharmacokinetics, fewer drug-drug and drug-food interactions, and reduced bleeding risks (1, 2). A major benefit of DOACs is that their use does not require routine laboratory monitoring for dose adjustment. There are certain clinical situations in which DOAC measurement may be beneficial, but quantitative assays to measure DOACs are not widely available. Increased availability of standardized DOAC assays may be helpful to ensure efficacy and safety of DOACs. In this article we will review DOACs, discuss clinical scenarios in which laboratory testing of DOAC may be useful, and review currently available tests for DOAC monitoring.

DOAC Characteristics

DOACs prevent coagulation and clotting by inhibiting specific factors of the coagulation cascade, namely factor Xa and factor IIa (thrombin). The sites of action for DOACs within the coagulation cascade are depicted in Fig. 1.

The direct thrombin inhibitor, dabigatran, is administered as a prodrug-dabigatran etexilate and must undergo conversion by liver carboxylesterases to its active form, dabigatran. Administration as a prodrug is necessary because of the low oral bioavailability (3%) of dabigatran. Relying primarily on renal excretion (~80% unchanged and ~4% active glucuronides), dabigatran may not be an ideal choice of therapy for patients with renal insufficiency (3). Factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) selectively and directly block the active site of factor Xa to inhibit conversion of prothrombin to thrombin. Rivaroxaban has high bioavailability and metabolism of rivaroxaban proceeds through cytochrome P450 3A4 (CYP3A4) to form inactive metabolites. Approximately 33% of the parent drug undergoes renal excretion. Apixaban is rapidly absorbed through oral routes (50% bioavailability) and is also partially metabolized by CYP3A4 to inactive metabolites, with approximately 27% renal elimination of the unchanged parent drug. Edoxaban has an average oral bioavailability of 62% and is minimally metabolized with approximately 50% clearance through renal elimination. Since all DOACs undergo renal elimination to some extent, dose reduction is indicated in patients with clinically significant renal impairment. A 2017 study found that a high percentage of patients with a renal indication for DOAC dose reduction remained overdosed with increased risk for bleeding (4). The same study found that a significant percentage of patients without a renal indication for dose reduction were

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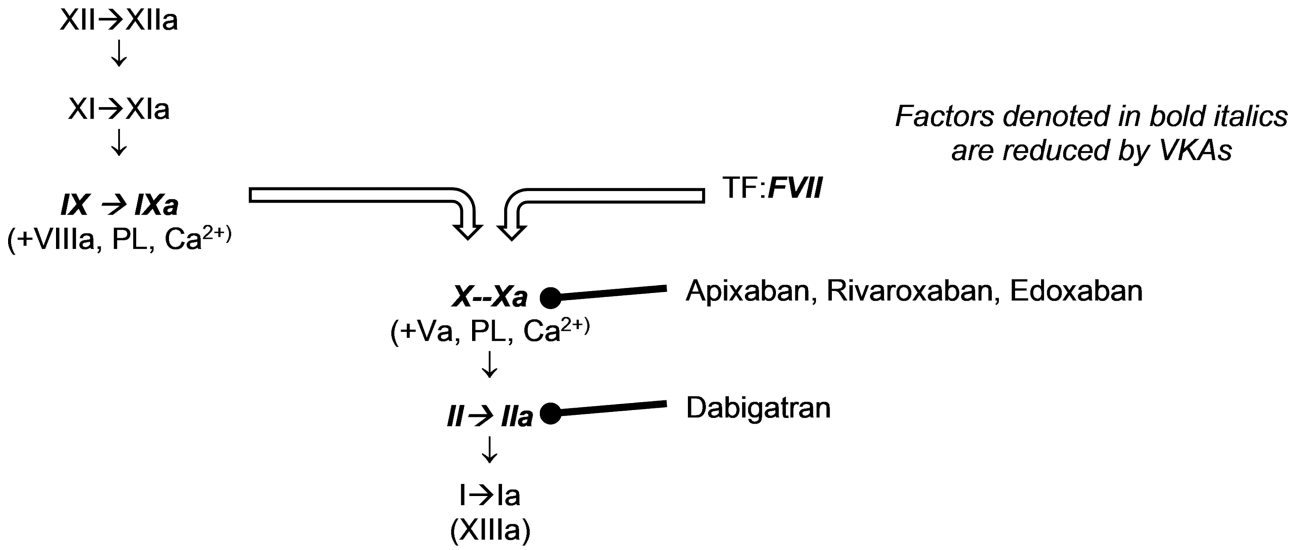

Fig. 1. Simplified coagulation cascade showing sites of action of the DOACs and vitamin K antagonists (VKAs). DOACs prevent coagulation and clotting by inhibiting specific factors of the coagulation cascade, namely factor Xa (e.g., rivaroxaban, apixaban, and edoxaban), or in the case of dabigatran, by inhibiting thrombin, which is also referred to as factor II.

actually underdosed, leading to increased risk for stroke. However, interpretation of DOAC levels is complicated since the major clinical trials did not monitor therapeutic ranges. Expected therapeutic ranges and a summary of DOAC characteristics are shown in Table 1 (5, 6).

Drug Levels and Decision Making

Certain clinical situations may benefit from measuring DOAC plasma concentrations, including decisions to withhold or administer reversal agents before emergent surgery, in cases of suspected overdose, during unexpected bleeding or thromboembolic events, and in patients with acute kidney or liver failure (7). Most patients using DOACs who require temporary interruption for a planned, non-emergent surgery can be managed using an interruption protocol, when the patient stops taking the drug for a specified period of time, generally 48 h. Those with acute changes in renal function, particularly if they are on dabigatran, may benefit from preoperative testing to ensure drug effect has waned prior to proceeding. Testing would be most beneficial for those undergoing higher risk procedures. Other circumstances where drug level testing might be considered include liver disease, drug-drug interactions, and stage V chronic kidney disease. In such patients, confirming that peak and trough levels are within expected ranges may provide reassurance that dosing is appropriate. If outside expected ranges, then conversion to a different DOAC or VKA may be considered (8). Additional indications for monitoring include advanced age, a body mass index above 40 kg/m^2, and in cases of suspected

Table 1. Expected therapeutic ranges and a summary of DOAC characteristics.

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Mechanism	Inhibits thrombin	Inhibits factor Xa		
Renal clearance	~80% renal	~27% renal	~50% renal	~33-67%
Half-life[a]	12-14 h	12 h	10-14 h	5-13 h
Dosing[b]	150 mg qd	5 mg bid	60 mg qd	20 mg qd
Expected peak conc. (range)[c]	175 ng/mL (117-275)	171 ng/mL (91-321)	170 ng/mL (125-245)	249 ng/mL (184-343)
Expected trough conc. (range)[c]	91 ng/mL (61-143)	103 ng/mL (12-137)	36 ng/mL (19-62)	44 ng/mL (12-137)

[a] Assumes normal renal function.
[b] Doses and plasma ranges listed are relevant to stroke prevention in non-valvular atrial fibrillation. Values may be different in prevention of pulmonary embolism, venous thromboembolism, or other indications utilizing different doses. qd = once daily; bid = twice daily.
[c] Statistics for expected peak and trough plasma concentrations and ranges (in percentile unless noted) varies by drug: Dabigatran: mean (25th–75th); Apixaban: median (5th–95th); Edoxaban: median (1.5 interquartile range); Rivaroxaban: mean (5th–95th).

Table 2. Potential Utility of DOAC level measurement in emergency and non-emergent situations (16) and scenarios when DOAC level monitoring may be considered.

Clinical Scenario	Laboratory Assay Result	Action
Emergent[a]		
Major bleeding[a]	DOAC level >50 ng/mL or qualitative = detectable	Consider reversal
Urgent surgery[a]	DOAC level >30 ng/mL or qualitative = detectable	Consider reversal or postpone surgery
Ischemic stroke[a]	DOAC level <30 ng/mL	Proceed with IVT[b]
	DOAC level 30–100 ng/mL	Consider IVT
	DOAC level >100 ng/mL	Consider non-IVT treatment
	No drug specific assay available	Consider non-IVT treatment
Non-emergent		
Drug Interaction	Quantitative DOAC level in range	No DOAC adjustment
Liver Impairment	Quantitative DOAC level out of range	Adjust or change DOAC
Renal Insufficiency		
GI/Malabsorption		
Body weight extremes		

[a] Applicable primarily when turnaround time for DOAC level <1 h, or available within the decision-making window.
[b] IVT = intravenous thrombolysis.

drug-drug interactions (5). It has also been proposed that increased availability of standardized DOAC assays may have the potential to improve efficacy and safety of these drugs in a number of other scenarios (9).

Reversal Agents for the Oral Anticoagulants

In patients requiring urgent surgery, or in those with life-threatening or uncontrolled bleeding, a reversal agent may be considered, specifically Praxbind (idarucizumab) or Andexxa [coagulation factor Xa–(recombinant), inactivated-zhzo]. Idarucizumab is a humanized monoclonal antibody fragment that outcompetes endogenous thrombin for binding of dabigatran and its glucuronide metabolites (10). Andexxa is a genetically modified factor Xa decoy molecule that binds and sequesters anti-Xa inhibitors (11).

Reversal of anticoagulation with these agents restores patients to baseline thrombotic risk.

In 2016 the International Society for Thrombosis and Haemostasis (ISTH) recommended a DOAC concentration greater than 50 ng/mL in the setting of serious bleeding as permitting administration of a reversal agent. In the same guidance, the ISTH identified non-bleeding patients requiring urgent surgery as potentially eligible for reversal if DOAC concentration is greater than 30 ng/mL (10). This latter group was also studied in Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE), where an acceptable preoperative concentration of less than 50 ng/mL was proposed (12). In the absence of available testing antidotes reversal is guided by the time since the last intake of the DOAC, and determination of the creatinine clearance, which influences the half-lives of the DOACs.

Utilization of idarucizumab and Andexxa is also limited by other factors. First among these is the high cost of these agents. The cost of reversal of DOAC effect for idarucizumab and Andexxa has been estimated to be $3500 and $58,000 per reversal, respectively (13, 14). Second, not all hospital pharmacies stock these antidotes and a patient may therefore present without having a specific antidote available. Third, administration of the specific antidote may not stop bleeding in all patients and may be associated with thrombosis in some. Due to the costs and concerns involved, utilization of laboratory testing to guide administration of reversal agents and other clinical decisions has been proposed (8, 15). Table 2 lists clinical scenarios where DOAC monitoring may be considered (16).

Laboratory Monitoring

Monitoring DOAC concentration is dependent on quantitative (direct measurement of plasma drug levels), and qualitative assays (which act as a screening assay).

Qualitative Assays

Qualitative tests include clot-based hemostasis methods such as prothrombin time (PT) and activated partial thromboplastin time (aPTT). Due to their direct effect on factors IIa and Xa, DOACs interfere with most clot-based methods; however, research has shown that the readily available coagulation tests such as PT and aPTT have low sensitivity for DOACs and the effect of different DOACs on PT and aPTT is reagent dependent. It is important to note that DOAC may also affect modified PT and aPTT assays (including other factor assays), dilute Russell's viper venom time, and chromogenic assays (antithrombin), which should be considered in the interpretation of laboratory results. The thrombin time (TT) is highly sensitive to dabigatran levels below 30 ng/mL, therefore a normal TT can be used to exclude the presence of residual dabigatran but cannot be used to confirm or estimate its plasma concentration.

Point-of-Care Assays

Rapid turnaround time is desired when screening and testing for DOAC in emergent scenarios, such as in cases of life-threatening bleeding or when emergent surgery is required for patients on DOACs. Point-of-care testing using nonspecific methods such as PT or aPTT suffer from the issues and challenges described for laboratory-based screening methods. Viscoelastic point of care methods (thromboelastograph, TEG and rotational thromboelastograph, ROTEM) have shown strong correlation with DOAC levels in some studies, but insensitivity in others, therefore additional studies are needed. Screening assays to detect DOAC in urine have also been evaluated, but do not correlate with serum levels. Early experience is growing with a qualitative urine dipstick technology (DOASENSE, GmbH) that may provide information on the presence or absence of DOAC within 10 min; however, currently the test is only available in Europe. A rapid point-of-care assay that can reliably determine DOAC levels in whole blood is currently needed.

Quantitative Assays

Direct measurement of DOAC levels can be accomplished using drug-calibrated chromogenic assays, drug-calibrated clot-based assays, and liquid chromatography tandem mass spectrometry (LC-MS/MS).

Chromogenic Assays for Assessment of Anti-FXa Levels (Rivaroxaban)

A chromogenic anti-Xa activity assay can be used to assess anti-FXa inhibitor effect across a wide range of concentrations. There are commercially available anti-Xa activity assays which measure factor Xa inhibition by the amount of chromogenic substrate that is cleaved by factor Xa, however only one is FDA approved (HemosIL Liquid Anti-Xa). Although these tests can potentially provide rapid turnaround time and can achieve lower limits of detection (<30 ng/mL), they can be confounded by multiple outside elements, most notably the presence of heparin (17). Finally, it is important to differentiate these anti-FXa activity level tests from tests that measure the factor X level, which does not assay inhibition of factor Xa. Chromogenic anti-FXa activity level tests require drug specific calibrators, and a unique test must be implemented for each factor Xa inhibitor. Recent reports of CAP proficiency testing for chromogenic assays measuring rivaroxaban showed good interlaboratory coefficient of variation (CV) for drug concentrations of 200 ng/mL and 400 ng/mL (within 10% CV) although performance at 50 ng/mL was classified as intermediate to poor (14).

Assays for Assessment of Anti-FIIa (Dabigatran)

Anti-FIIa inhibitors such as dabigatran may be quantitated by use of Ecarin based assays or a drug specific dilute thrombin time assay (dTT). Ecarin is an enzyme derived from the venom of the saw-scaled viper, *Echis carinatus*, that cleaves prothrombin into meizothrombin–a proteinase that induces clotting by cleaving fibrinogen to fibrin. Ecarin is inhibited by direct thrombin inhibitors (e.g., dabigatran) in a predictable linear fashion while being unaffected by the presence of heparin, warfarin, or lupus anticoagulant, and is specific for anti-FIIa activity. The Ecarin chromogenic assay (ECA) is most widely used. Dilute thrombin time (dTT) may also be used to quantitate dabigatran levels. This is a modified thrombin time method and requires drug-specific calibration. Unfortunately, none of these tests are routinely available in clinical settings.

Liquid Chromatography-Mass Spectrometry (LC-MS/MS)

LC-MS/MS is considered the gold standard for measurement of DOAC plasma concentrations, with reported measurement ranges spanning at least 5 ng/mL to 500 ng/mL. Protein precipitation and possibly phospholipid removal pre-treatments may be needed to alleviate matrix effects prior to analysis. Stable-isotope labeled DOACs are commercially available. A confounding issue for LC-MS/MS is that active parent drug and active metabolites must be monitored, when applicable. For example, active dabigatran is metabolized by UGT2B15 into dabigatran glucuronide–an active metabolite. Anti-FXa drug edoxaban also has an active M4

metabolite (5). Another challenge for LC-MS/MS standardization is the lack of internationally recognized reference materials.

In the case of life-threatening bleeding or acute stroke management results would need to be available, ideally within 30 min, which would be challenging for LC-MS/MS analyses. Rapid or expedited LC-MS/MS assays are currently performed for immunosuppressants and urine drug testing by some laboratories and the number of laboratories that have the ability to offer rapid testing by LC-MS/MS is increasing. Expedited and routine LC-MS/MS methods will still be valuable for non-emergent indications. Many toxicology laboratories have the necessary equipment to provide such testing, and the expertise needed to implement laboratory developed tests. Given that there are currently few options for quantitation of DOAC, particularly in the low range of <50 ng/mL, it seems likely that LC-MS/MS applications will be clinically useful. More recent advancements in the field of LC-MS/MS based therapeutic drug monitoring, including internal calibration approaches, is leading technological advancement in this area (18). These types of approaches, combined with commercially available reference standards, may make LC-MS/MS quantitation of DOAC achievable by a wider breadth of laboratories.

Conclusion

In contrast to VKAs, DOACs do not generally require routine laboratory monitoring. Certain circumstances may benefit from assessment of DOAC levels. Quantitative assays are not widely available for clinical use, and currently existing chromogenic based assays are less sensitive for low concentrations and are not entirely specific, although they may be adequate. DOAC laboratory monitoring, based on emergent (major bleeding or urgent surgeries) and elective indications (drug-drug interactions, body weight extremes, or renal and liver failure) in conjunction with monitoring steady-state peak and trough levels may assist clinical decision making to optimize patient management; however, increased availability of quantitative assays and additional studies that evaluate the utility of DOAC monitoring are needed.

Learning Objectives

After reading this article, the reader will be able to describe clinical scenarios where laboratory monitoring of direct oral anticoagulants (DOAC) may be useful. The reader will be able to discuss the currently available laboratory testing for DOACs.

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Recent CDC Updates on Blood Lead Reference Value in Children and the Potential Challenges to Testing Laboratories

By Nazmin Bithi, PhD and Yifei K. Yang, PhD

Adverse Impacts of Lead Exposures to Pediatric Populations

Lead is a naturally occurring heavy, bluish-gray metal with a low melting point, and is ubiquitously found throughout the earth with no recognized biological function (1). Lead was once used in various industries for paint, plumbing, batteries, gasoline, and cosmetics production. Lead-based paints were banned for residential use in 1978 in the US, and in 1996, leaded gasoline was banned for use in new vehicles. Currently, common sources of lead exposure include lead-based paint in houses built prior to 1978, contaminated soil, children's toys, jewelry, drinking water from corrupted pipes, workplace and hobby hazards, traditional home remedies and cosmetics, lead glazed ceramic ware, pottery, leaded crystal, and imported candy (2). Lead produces a neurotoxic effect in the brain and can impact behavioral and nerve cell development (3). Adverse effects of lead exposure can range from subtle responses to overt toxicity, depending on the amount of lead that is absorbed into the body and the age and health status of the person. During development, babies and young children are more vulnerable to the damaging effects of lead because of their undeveloped blood-brain barrier and rapidly developing nervous system. Children absorb lead 5 times more efficiently from the gastrointestinal tract compared to adults. Children under 6 years of age are especially at a higher risk of lead exposure. Lead still poses a significant health threat to this pediatric population, despite the observation that blood lead levels (BLL) in epidemiology studies have been gradually lowered over time (2, 3). Even at low concentrations, lead exposure can cause lower intelligence quotient (IQ) and decreased focus and may ultimately damage academic performance outcomes. In the US, vulnerable populations from low-income households and living in older housing are at the highest risk for potential lead exposure
(2, 4).

Lowering the Threshold to Detect More Lead Exposure in Vulnerable Populations

Because of the adverse developmental impacts, there is no safe BLL for children. The American Academy of Pediatrics and the Centers for Disease Control and Prevention (CDC) guidelines recommend screening for all Medicaid-eligible children who are under high-risk groups (1, 5). A survey on 2018 US-born children indicated that preventing and/or maintaining lower blood lead exposure could save approximately $23.5 billion in costs associated with health care, educational support, and the juvenile justice system over their lifetimes (4). In 2012, the CDC adopted the recommendation by the Advisory Committee on Childhood Lead Poisoning Prevention and introduced blood lead reference value (BLRV) to replace the term "level of concern" to identify lead exposure in children (6). The BLRV does not indicate safe or toxicity thresholds. A reference value is used for a chemical or substance that does not have any safe level and is defined as the statistical calculation of concentration distribution compared to the population mean value. For BLRV in children, the level is based on the 97.5th percentile of the blood lead concentration distribution among US children between 1 and 5 years of age (6). Based on the National Health and Nutrition Examination Survey (NHANES) data, the overall BLLs in all age groups have been decreasing since 2012 (3). In 2012, the CDC recommended BLRV at 5 μg/dL based on NHANES data from the 2007-2010 cycles. Based on NHANES data collected from 2015-2018 and recommendation made by the Lead Exposure Prevention and Advisory Committee (LEPAC), the CDC further lowered the BLRV for children in October 2021 to 3.5 μg/dL as a value that needs to be implemented in clinical practice (7).

Analytical and Technical Challenges to the Testing Laboratories

Blood lead testing is the most effective way to identify lead exposure due to the asymptomatic nature for most children after exposure (4, 6). Nevertheless, it remains a challenge for clinical laboratories to meet the required analytical accuracy and imprecision when measuring blood lead at such low concentrations (5). Based on recent blood lead proficiency testing survey administered by the College of American Pathologists (CAP), atomic absorption spectroscopy (AA) and inductively coupled plasma mass spectrometry (ICP-MS) are the 2 methodologies adopted by most laboratories, with a small fraction of the participating laboratories still utilizing anodic stripping voltammetry-based methods, such as Magellan LeadCare products. Based on the CDC's Lead and Multielement Proficiency (LAMP), these methods should have quantification ranges compatible with the lowered BLRV (8). The accuracy of these methods may vary within the reportable ranges, especially near the lower limit of quantification. In children, initial screening is normally performed with a fingerstick capillary sample and confirmed with a separate venous sample when the initial result is elevated. In an ICP-MS based assay, following sample collection, the whole blood sample is added to a diluent solution containing internal standards, stabilizer, and matrix modifiers. For analysis and quantification, the specimen mixture is aspirated and automized into a precalibrated ICP-MS analyzer. A calibration curve is applied for quantitation by adding a constant amount of internal standard added to calibrators, quality control samples, and patient samples. For blood lead, most ICP-MS methods should have lower limit of quantification (LLOQ) <3.5 μg/dL (8). For clinical reporting, quantified results lower than the assay's LLOQ are reported as < LLOQ. Depending on individual clinical laboratory practice, a quantified value reported between the LLOQ and BLRV may not necessarily trigger a warning flag in the electronic medical record system.

Recent CDC publications have reported that approximately 2.5% of children 1-5 years old in the US have blood lead level ≥3.5 μg/dL (3, 7). Lowering the BLRV from 5 to 3.5 should help to identify more children at risk for lead exposure and initiate timely intervention. Based on the retrospective and de-identified aggregate data from ARUP Laboratories, we examined blood lead levels from over 2000 venous collection specimens from different age groups submitted for clinical assessment and measured by an ICP-MS method with an LLOQ of 2 μg/dL. In the age group "under 6 years old," there are approximately 4.3% of the samples with BLL ≥5 μg/dL. There are approximately 6.8% samples with BLL ≥3.5 μg/dL (Table 1). Based on the LLOQ of 2 μg/dL, 88.5% of the results in this age group are lower than the assay's reporting limit. Although the recommendation is focused on children between the age of 1 and 5 years old, we also investigated the impact of lowering the reference level value for age groups "6-11 years old" and "18 years old and above" (Table 1). Similar to the NHANES study results (3), in children between 6 and 11 years old, a smaller proportion (3.3%) of the BLL results are ≥5 μg/dL compared to the age group 1-5 years old. If the 3.5 μg/dL and above threshold is adopted, an additional 2.4% of the samples would be identified as lead exposure cases. In the adult group (18 years old and above), 3.5% of the samples contain BLL ≥5 μg/dL, as 5 μg/dL is still considered to be case classification for an elevated BLL for surveillance purposes (9). In the same adult age group, 5.4% of the results are ≥3.5 μg/dL.

Table 1. Percentages of blood lead results as elevated based on BLRVs of 3.5 and 5 μg/dL

Age group	Results ≥3.5 μg/dL	Results ≥5 μg/dL
Under 6	6.77%	4.34%
6-11	5.76%	3.30%
18+	5.43%	3.47%

Conclusions

The BLRV in children between 1 and 5 years old has been lowered to 3.5 μg/dL (from 5 μg/dL) by the CDC based on the epidemiology data over the past 10 years (3). Despite the declining geometric mean of BLL in US pediatric populations, certain groups of children suffering from structural inequities and environmental prejudices still remain at substantial risk for lead exposure. Laboratory lead testing plays a vital role in detection and successive management of lead exposures. Therefore, decreasing BLRV can identify significantly more numbers of children with lead exposure. Public health and clinical laboratories might face technical and analytical challenges, as well as opportunities to adopt the new BLRV for children. Depending on assays and methodologies adopted, laboratories may need to improve accuracy and precision near the lower limit of quantification for their laboratory developed tests based on the new reference value, adjust their reporting limit policies, and may purchase new and advanced instrumentation. It is important to optimize the testing practices to meet proficiency testing criteria to measure BLLs at 3.5 μg/dL. Early detection of lead exposure will help

clinical providers and families to intervene by identifying sources of exposure and removing them; therefore, this action may help to limit or prevent potential adverse health effects of lead.

Learning Objectives

After reading this article, the reader will be able to list the adverse neurological and developmental impacts of lead exposure and toxicity, understand the downward trends of blood lead levels in the US population and the persistent risks of lead exposures in vulnerable populations, and describe the analytical challenges of testing laboratories associated with the decreased blood lead reference value in children.

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Dr. Bithi discloses salary/consultant fee from ARUP. Dr. Yang has nothing to disclose.

Society of Forensic Toxicologists (SOFT) Annual Meeting 2021 Highlights

By Jennifer Colby, PhD, DABCC

The 2021 annual meeting of the Society of Forensic Toxicologists (SOFT) was held September 26 to October 1, 2021, in Nashville, TN. Since the 2020 annual meeting was held virtually, this in-person event was a welcome opportunity to get together with colleagues and friends. The approximately 700 attendees gathered at the Gaylord Opryland Hotel and Convention Center, a resort property located a short drive from downtown Nashville.

As is typical for a SOFT meeting, scientific content was delivered through workshops, posters, and platform presentations. Before the start of the formal meeting, SOFT attendees were treated to a full slate of 11 workshops, including a very highly attended workshop on drug interactions, chaired by Robert Kronstrand and Rebecca Hartman, and several workshops on alternate matrices. The scientific sessions began on Wednesday, September 29th, with a plenary lecture delivered by Dr. Matthew Johnson of Johns Hopkins, who spoke on the use of psychedelics in clinical medicine.

Following Dr. Johnson's lecture, SOFT President, Past President, and the chair of the history committee awarded medallions to all SOFT Past Presidents in attendance. The medallions are a new tradition that will continue in future years, serving as a visual reminder for meeting attendees to recognize Past Presidents for their service to SOFT. In addition to presidential medallions, SOFT implemented 4 new awards in 2021. The first Research in Forensic Toxicology Award was presented to Alex Krotulski, the first Young Forensic Toxicologist Award was presented to Dani Mata, the first Teaching and Mentoring Award was presented to Michelle Peace, and the final award, the Distinguished Service Award, was presented to Chip Walls. These awards are in addition to the traditional Leo Dal Cortivo awards for best poster presentation and best platform presentation, the educational research awards, and the young scientist meeting awards.

The overall scientific program of the meeting featured 9 platform sessions. Topics were varied and included assessment of drug stability in various matrices, detection of novel psychoactive substances, drug-facilitated crimes, various case reports, and drugs and driving. The program also included 2 poster sessions with a total of nearly 80 posters. The poster session featured presentations on beta glucuronidase, method validations using LC-MS/MS, GC-MS/MS, and GC-FID techniques, and many interesting case studies. One of the highlights of the SOFT meeting is always the Elmer Gordon forum, where attendees gather to discuss regular casework findings. At this year's meeting, the conversation focused on the evolving landscape of cannabinoids. Specific topics included Δ8-THC, Δ10-THC, THC-O-acetate, and tetrahydrocannabiphorol (THC-P). Many attendees expressed their hope for the availability of reference materials for metabolites of these compounds.

Although sharing scientific findings is the primary purpose of the annual meeting, SOFT attendees took advantage of being together to network and socialize. Despite the uncertain travel and coronavirus disease situations, most regular exhibitors attended the meeting. Attendees visiting their booths were treated to great networking opportunities and a scavenger hunt. Tradition dictates an offsite social event, which was held in downtown Nashville at Pinewood Social. The indoor/outdoor environment was well received by attendees. The theme for this year's SOFT Presidential Reception was Rhinestone Toxicologists, and attendees came dressed in their finest rhinestone gear (including bedazzled face masks!). Attendees danced the night away to the sounds of the 10-piece Downtown Band. With all the musical talent in Nashville, it is no surprise that the band was an attendee favorite.

Learning Objectives

After reading this article, the reader will be able to list scientific focus areas from the 2021 annual meeting of SOFT.

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The author has nothing to disclose.

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Learning Objectives

Learning objectives vary by article, but in general, after completing *Clinical & Forensic Toxicology News*, the reader will be able to:

- Describe emerging and changing trends in drug abuse, including new designer drugs, usage patterns, and contaminants/adulterants.
- Identify potential analytes (drugs, metabolites, biomarkers) of clinical and/or forensic significance.
- Evaluate methodologies for their utility and limitations relative to the needs of toxicology labs.
- Discuss relevant regulations, such as analytical performance requirements, or the legality of new drugs of abuse.
- Explain the analytical and regulatory issues unique to specific applications, including postmortem toxicology, workplace drug testing, and drug screening.
- Describe the medical implications of drug abuse, toxicity associated with therapeutic agents, and exposure to other toxicants.

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