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Special Report

National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Recommendations for the Use of Laboratory Tests to Support Poisoned Patients Who Present to the Emergency Department

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Background: **Exposure to drugs and toxins is a major cause for patients' visits to the emergency department (ED).**

Methods: **Recommendations for the use of clinical laboratory tests were prepared by an expert panel of analytical toxicologists and ED physicians specializing in clinical toxicology. These recommendations were posted on the world wide web and presented in open forum at several clinical chemistry and clinical toxicology meetings.**

Results: **A menu of important stat serum and urine toxicology tests was prepared for clinical laboratories who provide clinical toxicology services. For drugs-of-abuse intoxication, most ED physicians do not rely on results of urine drug testing for emergent management decisions. This is in part because immunoassays, although rapid, have limitations in sensitivity and specificity and chromatographic assays, which are more definitive, are more labor-intensive. Ethyl alcohol is widely tested in the ED, and breath testing is a convenient procedure. Determinations made within the ED, however, require oversight by the clinical laboratory. Testing for toxic alcohols is needed, but rapid commercial assays are not available. The laboratory must provide stat assays for acetaminophen, salicylates, co-oximetry, cholinesterase, iron, and some therapeutic drugs, such as lithium and digoxin. Exposure to other heavy metals requires laboratory support for specimen collection but not for emergent testing.**

Conclusions: **Improvements are needed for immunoassays, particularly for amphetamines, benzodiazepines, opioids, and tricyclic antidepressants. Assays for new drugs of abuse must also be developed to meet changing abuse patterns. As no clinical laboratory can provide services to meet all needs, the National Academy of Clinical Biochemistry Committee recommends establishment of regional centers for specialized toxicology testing.**

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Preamble

This is the ninth in the series of Laboratory Medicine Practice Guidelines sponsored by the National Academy

of Clinical Biochemistry (NACB).[10] An expert Committee of emergency department (ED) physicians and clinical laboratory medicine toxicologists was assembled and prepared recommendations on the use of clinical laboratory tests to support the diagnosis and management of the poisoned patient who presents to the ED. Excluded from these discussions were drug testing conducted for the workplace, forensic and medical examiner toxicology, athletic drug testing, and testing for various compliance programs (e.g., criminal justice, psychiatric, and physician health). Many of these other programs are guided by other recommendations and regulations, such as the Substance Abuse and Mental Health Services Administration, the American Academy of Forensic Sciences, and the International Olympic Committee. Recommendations for detection of drugs in pregnant women and newborns exposed during the intrauterine period are discussed in a previous NACB guidelines *(1)*. Some of the recommendations contained here are directed specifically toward manufacturers of toxicology reagents. It is hoped that documentation of a clinical need for modified assays will encourage manufacturers to develop these new and improved assays.

These recommendations were presented in open forum at several meetings during the year 2001: a local clinical chemistry section meeting at the Royal Brisbane Hospital (Brisbane, Australia) in January; the Midwest Association for Toxicology and Therapeutic Drug Monitoring, William Beaumont Hospital (Royal Oak, MI), in May; Edutrak Sessions at the AACC Annual Meeting (Chicago, IL) in August; and in October, The North American Congress of Clinical Toxicology (Montreal, Canada), The Society of Forensic Toxicology (New Orleans, LA), and the Scientific Assembly Toxicology Section meeting of the American College of Emergency Physicians (Chicago, IL). Participants at each meeting discussed the merits of the recommendations. A summary of these discussions are presented herein.

These guidelines cover four major areas. The section on each recommendation contains background information and summarizes the discussions by the Committee and participants of the various sessions on the rationale for that recommendation. We also provide qualitative ratings for the degree of consensus for adoption of the recommendations, based on discussions among the participants at the various presentations and correspondence received: "A" indicates general consensus by most participants, whereas "B" indicates either no consensus or that the recommendation was not applicable to all situations.

[10] Nonstandard abbreviations: NACB, National Academy of Clinical Biochemistry; ED, emergency department; DAWN, Drug Abuse Warning Network; NPIS, National Poisons Information Service; ACB, Association of Clinical Biochemists; TCA, tricyclic antidepressant; LSD, lysergic acid diethylamide; GHB, γ-hydroxybutyrate; TAT, turnaround time; POC, point-of-care; GC, gas chromatography; MS, mass spectrometry; PCP, phencyclidine; THC, tetrahydrocannabinol; FDA, Food and Drug Administration; QA, quality assurance; QC, quality control; CNS, central nervous system; PT, prothrombin time; EPP, erythrocyte protoporphyrin; TIBC, total iron-binding capacity; UIBC, unsaturated iron-binding capacity; and RBC, red blood cell.

Introduction and Needs Assessment

Data from the Drug Abuse Warning Network (DAWN) have shown that a significant number of ED visits are associated with the presence of alcohol and drugs as indicated by history *(2)*. Table 1 lists results for 2002. The statistics refer to patients 6–97 years of age whose primary presenting problem was associated with drug use but was not necessarily the sole reason for the ED visit. This database is not a measure of illicit drug or substance abuse prevalence in the general population. Moreover, these statistics are based on self-reporting by the user and were not necessarily confirmed by laboratory testing. Some drugs (e.g., cocaine and heroin) may have a higher association with ED visits than others because they produce greater acute toxicity. Alcohol is not tabulated separately by DAWN; however, many studies have demonstrated a high prevalence of alcohol and substance abuse in ED patients, particularly trauma patients. Prevalence rates of ~25%, along with other data, suggest that nearly 30 million ED visits per year could be associated with some form of drug use *(3)*.

There are other substances that can contribute to significant acute clinical problems for which laboratory testing might play an important role. Some of these are tabulated each year by the Toxic Exposure Surveillance System of the American Association of Poison Control Centers *(4)*. In 2000, for example, there were 13 000 reported exposures to organophosphorus compounds, 16 000 to rodenticides (anticoagulants), 12 500 to heavy metals, 17 000 to carbon monoxide, and 1000 to toluene. It should be noted that the majority of these exposures were

Table 1. Estimated number of ED drug episodes and drug mentions, 2001.[a]

Drug or class	% of total ED visits
Alcohol-in-combination	0.218
Cocaine	0.193
Marijuana/hashish	0.111
Benzodiazepines (alprazolam, diazepam, lorazepam, clonazepam, triazolam)	0.103
Analgesics (acetaminophen, aspirin, ibuprofen, propoxyphene, oxycodone, hydrocodone)	0.099
Heroin/morphine	0.093
Amphetamines (amphetamine and methamphetamine)	0.034
Barbiturates (phenobarbital, over-the-counter sleep aids)	0.018
TCAs (amitriptyline, doxepin, imipramine)	0.012
PCP	0.006
Lithium	0.003
GHB	0.003
LSD	0.003

[a] From the Office of Applied Statistics, the DAWN, 2001. Total ED visits, 100.5 million; number of drug episodes, 638 484; drug mentions, 1 165 367.

managed in a non-healthcare facility, usually at the site of exposure.

There will always be pressure between the need to make decisions quickly in the ED setting and the availability of reliable information to guide those decisions. This is true for all aspects of care, from obtaining a history and physical exam to laboratory testing and evaluating response to therapy or likely course of illness and future care. With regard to analyses performed in toxicology laboratories, it is known that a thorough toxicology screening incorporating various methods can identify many more substances than are clinically suspected. At the same time, this information often has no clinical utility because of the time required for specimen delivery, preparation, analysis, and reporting or because the presence of the substance is inconsequential. This has contributed to a range of clinical opinions and practices, from a minimalist approach to a "shotgun" approach of broad-based laboratory testing. These guidelines can be used to discuss the pros and cons of both approaches.

Finally, these recommendations identify laboratory support measures that can improve patient care. They will need to be adapted to specific situations, such as the evaluation of possible child abuse or so-called emergency psychiatric clearance. They do not address every question or identify every substance that might cause an individual to seek emergency care. For example, certain substances are explicitly identified as not requiring stat analytic identification, whereas many are not mentioned at all. The former are often agents that manufacturers have historically included on instrument menus or that certain third-party regulators or agencies have required. When there is no current rationale for these practices, we hope this document can be used cooperatively by laboratory and ED directors and their respective organizations in concert with manufacturers to make changes locally and nationally. On the other hand, these recommendations are designed to be useful to the ~30 000 physicians making decisions in EDs across the US. As such, they do not represent the minimum laboratory evaluation that may be used by a specialist in medical toxicology, nor do they reflect all of the current analytic limitations present in various areas of the country. However, they can serve as a forum for discussion of the toxicology laboratory support that can and should be provided within a given patient population, institution, or geographic region of the country.

Part I. General Principles for Drug Testing to Support ED Toxicology

A. TIER I TOXICOLOGY TESTING

Introduction. Because of considerable limitations in resources and existing technology, it is impossible for any clinical laboratory to provide a full spectrum of toxicologic analyses for the impaired or overdosed patient in real time. Given this limitation, it is appropriate to make recommendations as to which serum or plasma and urine tests have the greatest impact on patient management and can be realistically delivered.

Table 2. Stat quantitative serum toxicology assays required to support an ED.[a]

Acetaminophen (paracetamol)
Lithium
Salicylate
Co-oximetry for oxygen saturation, carboxyhemoglobin, and methemoglobin
Theophylline
Valproic acid
Carbamazepine
Digoxin
Phenobarbital (if urine barbiturates are positive)
Iron
Transferrin (or UIBC assay if transferrin is not available)
Ethyl alcohol
Methyl alcohol[b]
Ethylene glycol[b]

[a] TAT of 1 h or less.

[b] More realistic TATs for these assays are 2–4 h. These tests are largely unnecessary in countries where these agents are not widely available.

The basis and inclusive requirements behind the tests listed under the first tier include clinical relevance, available analytical assays for stat testing, and results that may have an immediate impact on subsequent management decisions or patient care. Management decisions need not necessarily relate to acute overdose therapy because results of urine drug testing are also used to determine admission to psychiatric wards. Given the problems with existing immunoassays with regard to sensitivity and specificity, the need for such drug testing is questionable if the patient is not in acute distress. Both falsely positive and negative results can lead to unnecessary investigations.[11]

Recommendation. The clinical laboratory should provide two tiers of drug testing. The first tier includes stat testing of selected target quantitative tests in serum or plasma (Table 2) and qualitative tests in urine (Table 3). If the patient is in no acute distress, additional or even most initial toxicology testing may be unnecessary. *Degree of consensus: A for the analytes listed in Table 2, B for the analytes listed in Table 3.*

Discussion. The need for stat quantitative serum or plasma assays was not heavily debated during the presentations. Testing for acetaminophen, salicylates, iron, co-oximetry, iron, and toxic alcohols is discussed in *Parts III* and *IV*. The toxicities and need for monitoring of the therapeutic

[11] In this document, the terms false positive and false negative refer to a test that is positive in the absence of the drug in question and negative in the presence of the drug in question, respectively. The ED staff may have other nonmatching definitions of these terms.

Table 3. Stat qualitative urine toxicology assays required to support an ED.[a]

Cocaine
Opiates
Barbiturates
Amphetamines[b]
Propoxyphene[b]
PCP[b]
TCAs[c]

[a] In general, urine toxicology screens such as these have a lower urgency and utility than do serum assays. They do not correlate well with clinical effects and suffer from problems with sensitivity and specificity, as discussed in the text. Although widely available, these assays (with the exception of that for the cocaine metabolite) require clinical interpretation.

[b] Need for these assays may be based on prevalence of drug use, which may vary from region to region. Regular review of drug usage is important.

[c] Recommended only if the clinical staff fully understands the specificity limitations of this assay, i.e., results are used in conjunction with the electrocardiograph to support a clinical suspicion of TCA toxicity, but not in cases where a positive urine drug test is the sole evidence for this suspicion.

drugs listed in Table 2 are not discussed in this document but are listed under the Tier I tests for completeness purposes. The Tier 1 stat quantitative serum/plasma toxicology test menu (Table 2) is nearly identical to a recent joint guideline published by the United Kingdom Group of the National Poisons Information Service (NPIS) and the Association of Clinical Biochemists (ACB) *(5)*. The differences are the inclusion of the anticonvulsants in the NACB guideline and the omission of paraquat, which was listed in the NPIS/ACB guideline. In the US, paraquat exposure is rare: there were 120 total reported exposures and no deaths in 1998 *(4)*.

In contrast to the situation with serum/plasma testing, the need for stat qualitative urine assays was questioned by many ED physicians. Discussion focused not only on which assays should be included or omitted, but the need for urine drug screening itself, given the inaccurate data that many immunoassays provide and a perceived lack of impact on acute patient care. The finding of a positive result in urine may be completely incidental to the presentation given the lack of an association between clinical impairment and the presence of a drug or its metabolite in urine and considering the length of time that the drug or analyte may be detectable in urine (2–30 days or more depending on the analyte and use pattern). As such, this document's conclusions are in disagreement with the Laboratory Guideline for the Investigation of the Poisoned Patient prepared by the Alberta Medical Association (Alberta, Canada), which recommended that "A nonspecific toxicology screen is of limited value in the majority of cases and is rarely indicated" *(6)*. The NPIS/ACB have recommended that urine toxicology screens be listed under the category of specialist or infrequent assays *(5)*. The Medicare Carrier Advisory Committee have recently proposed a policy that a qualitative drug screen is not medically reasonable or necessary in known overdose cases when the patient is asymptomatic (i.e., responsive to verbal stimuli and has no seizures, hypoventilation, or cardiac abnormalities other than sinus tachycardia after several hours of observation). Although the NACB Committee agrees in principle with these guidelines and recommendations, the Committee is also of the opinion that few EDs and clinical laboratories will abandon their reliance on urine drug screens on the basis of its recommendations. This may be particularly true in small or rural hospitals that do not have clinical toxicology specialists available who understand these analytical limitations. In addition, many practitioners utilize urine drug screens to increase their confidence in making diagnoses and disposition decisions. Therefore, if urine drug testing is inevitable, ED physicians and clinical laboratories should encourage the in vitro diagnostic industry to take steps to improve analytical methodologies so that they can deliver more accurate drug testing services for the identified drug class. Important issues include assay specificity, cross-reactivity studies, cutoff concentrations (and the definition of false positive and negatives), confirmation testing, and issues regarding chain of custody.

There was considerable debate as to the wisdom of including tricyclic antidepressants (TCAs) to the Tier 1 test list, given the poor specificity of existing immunoassays for TCAs. Despite these problems, the finding of a positive assay may increase the awareness of other possible ingested medications. Therefore, a qualifier has been included in Table 3 to indicate that this is an area where ongoing education of clinical staff is necessary for optimum utilization of this test. In the absence of such education programs, the ED staff might consider this test too inaccurate for naive users and choose to omit it in the Tier 1 panel. Another issue with TCA testing is the appropriate urine cutoff concentration. If the intent is to determine therapeutic and toxic concentrations, a low cutoff might be appropriate, such as 300 μg/L. If the intent is to detect toxic concentrations, which is the most likely the goal in the ED patient, then a cutoff of 1000 μg/L may be more appropriate. This latter cutoff might also reduce the number of false-positive urine drug results attributable to non-TCA drugs. A clinical evaluation of TCA cutoff concentrations in urine to justify these statements has not been published to date *(7)*. It is likely, however, that a single TCA cutoff consistent with toxicity cannot be established.

During the open discussion, a participant questioned the applicability of the Tier 1 test menu for pediatric patients. It is the opinion of the Committee that individual hospitals and medical centers should revise this list as appropriate to handle special populations and needs. Accidental overdoses of prescription or over-the-counter medications such as acetaminophen, salicylates, and iron tablets may be more of a concern in children than street drugs such as marijuana and cocaine, which are abused by older adolescents and adults. Fortunately, the implementation of "tamper-resistant" packaging has greatly

reduced the number of accidental poisonings by toddlers *(8)*. Other substances continue to be a problem for children under 6 years, including cosmetics, cleaning substances, foreign bodies, plants, topicals, cough and cold preparations, pesticides, vitamins, gastrointestinal preparations, antimicrobials, arts/crafts/office supplies, antihistamines, hormone and hormone antagonists, and hydrocarbons *(4)*. Results of drug testing can also have a forensic impact on allegations of child abuse or neglect and custody disputes for children and their caregivers.

Drugs-of-abuse patterns among teenagers and young adults may be dramatically different from patterns in older adults, e.g., abuse of lysergic acid diethylamide (LSD), methylenedioxymethamphetamine (Ecstasy), and γ-hydroxybutyrate (GHB). However, the frequency of ED presentation for acute care related to these drugs or the utility of an analytic tool in changing management do not justify their inclusion as a Tier 1 recommendation at this time. Proproxyphene use can contribute to significant toxicities, including cardiac arrhythmias, possibly delayed in appearance. Nevertheless, a laboratory may choose to exclude propoxyphene or any other drug from the Tier 1 list if the prevalence of this drug is low in the geographic region served by that laboratory. It should be noted that drugs that show geographic variability may change over time, requiring reevaluation by the clinical and laboratory staff.

At this time, the Committee does not recommend regular testing of urine for benzodiazepines until the problems with immunoassays, as discussed in *Part 2D,* are resolved.

It is also important to note that the list of tests shown in Tables 2 and 3 are analytes the laboratory should make available on a stat basis, allowing the causative agent to be identified when a patient presents with signs and symptoms suggesting exposure to one or more of these drugs. Tables 2 and 3 do not imply an ED panel of tests that should be ordered on all patients. The ED physician and toxicologist must decide on the most appropriate plan of action based on the clinical presentation on a case-by-case basis.

B. Assay Turnaround Times for Tier I Tests

Introduction. The recommended turnaround time (TAT) for reporting of assay results is a consistent theme among the previous NACB Laboratory Medicine Guidelines because it is readily quantifiable and is an area where most laboratories can find improvement. Among the factors important for achieving acceptable TATs for laboratory tests are the availability of resources, cooperation with the house staff, efficient specimen delivery systems, reductions in the complexity and number of steps in the preanalytical processes, effective laboratory and hospital information systems, and the establishment of a priority list of analytes considered critical to patient care.

Recommendation. The ideal TAT for Tier 1 toxicology tests is 1 h or less except where noted on Table 3. *Degree of consensus: B*

Discussion. Reporting TATs for laboratory tests continues to be a major issue for all stat testing, not just for drugs of abuse. The overwhelming majority of participants were in favor of the 1-h TAT. The major issue, however, is the appropriate definition of reporting TATs. Some felt that this should be defined from the time of specimen receipt within the laboratory to the availability of results, either by phone or via electronic reporting to the record. Others felt that the TAT should be defined from the time the test is ordered to the reporting time, although laboratory personnel may not have the responsibility of specimen collection and delivery to the laboratory. Nevertheless, proponents of this definition argue that the laboratory should take on this role or at least have some influence on this practice. An important part of meeting this expanded definition is the availability of a rapid specimen delivery system to the laboratory, i.e., a pneumatic tube or use of point-of-care (POC) testing within the ED. Without these conveniences, it is unlikely that clinical laboratories can meet the 1-h TAT as defined from the time of ordering and that the 1-h TAT might be better applied to the time of specimen receipt. Although toxicology data may impact on the efficiency of ED triaging decisions, most acute management decisions are based on the patient's vital signs and mental status, irrespective of what the laboratory results shows and when they are received.

A continuing issue that was raised in several sessions is the potential legal impact for institutions that are unable to meet the 1-h TAT. These guidelines were developed as goals in hope of providing justification for hospitals and laboratories to improve their testing services. The Committee reemphasizes that these recommendations are not standards of care and may not even be a consensus of the current practice; they, however, reflect ideal goals for both laboratory practice and incentives for the in vitro diagnostics industries.

C. Tier II Testing: Comprehensive or Broad-Spectrum Testing

Introduction. Stat testing is adequate to support ED evaluation of acute toxicity for the specific toxins listed in Tables 2 and 3 for which a specific therapy or antidote may be available. A second tier of more complicated and time-consuming tests is recommended for patients with continuing medical problems from toxicologic exposure to drugs and chemicals not identified in Tier I. General screening for a broad spectrum of toxins is generally not necessary for patients who are asymptomatic or clinically improving in the ED. In the event that a patient presents with or develops coma or other clinical signs that cannot be explained by one of the Tier 1 toxins, further evaluation by a trained clinical toxicologist is indicated. These evaluations usually occur outside the ED setting. The avail-

ability of tests for these toxins and their recommended TATs are different from those for Tier I tests. The laboratory should be advised if there is a need for a broader panel of tests.

Recommendation. The second tier of drug tests is for patients admitted to the hospital who remain intoxicated, obtunded, or comatose, where a broad-spectrum ("comprehensive") screening panel is necessary to cover drugs and substances that may have clinical significance and would not be identified based on the findings of the first tier of laboratory tests. Results of these tests might be used for more long-term management and/or counseling of patients. Laboratorians should work closely with intensive care providers to determine the appropriate menu of tests and TATs that are necessary. *Degree of consensus: B*

Recommendation. Testing for toxins beyond those outlined in Tables 2 and 3 should be performed only after the patient is stabilized and the attending physician has received toxicology input from a poison control center or, preferably, bedside evaluation by personnel trained in medical toxicology. *Degree of consensus: A*

Discussion. A two-tiered mechanism allows a laboratory to concentrate the majority of its resources on providing for the needs of the sick ED patient. The Committee has excluded certain drugs from the first tier of testing because they do not have significant toxicities or they are difficult to measure on a stat basis. These include the phenothiazines, calcium channel blockers, beta blockers, hypnotics and tranquilizers (e.g., chloral hydrate, ethchlorvynol, and glutethimide), some anticholinergic drugs (e.g., atropine), muscle relaxants (e.g., carisoprodol and cyclobenzaprine), some antidepressants (e.g., fluoxetine), behavioral drugs (e.g., clonidine and methylphenidate), date rape drugs (GHB and flunitrazepam), certain anesthetics (e.g., ketamine), and analgesics (fentanyl and analogs). Some of these drugs will be detected on the broad-spectrum tier of testing.

The issue of GHB testing was specifically raised during one of the sessions, i.e., "if a commercial immunoassay were available would there be requests for this test?" The majority of the AACC meeting participants thought that a test for GHB would not be used at their institutions. In general, the clinical presentation and course of this agent are characteristic and shorter than the usual assay TAT.

Methodologies for a comprehensive urine drug screen profile include thin-layer chromatography, liquid chromatography with full-scan spectrophotometric detection, gas chromatography (GC) with mass spectrophotometry (MS), and liquid chromatography–tandem MS. Hospitals that do not have adequate resources to perform a broad-spectrum screening panel can elect to send these specimens to a reference laboratory or regional toxicology laboratory (see *Part IV-K*). In this situation, laboratory personnel should ascertain the methodologies used by the reference laboratory, including the expected TATs and assay limitations, and communicate this information to the attending physician because this may have an impact on the interpretation of results.

D. SELECTIVITY OF TESTING

Introduction. It is not appropriate for the clinical laboratory to provide test results for all classes of drugs simply because an automated and inexpensive immunoassay is available. Certain tests may not be indicated because the substances they measure do not contribute to significant toxicologic sequelae or their prevalence in that particular geographic location is very low. There is the additional problem of diagnostic inaccuracy if these tests are included in a general drug-screening panel, particularly with tests for phencyclidine (PCP) and TCAs, because existing immunoassays exhibit significant cross-reactivity toward other drugs, e.g., dextromethorphan, diphenhydramine, and sertraline for PCP *(9)* and phenothiazines, cyclobenzaprine, and diphenhydramine for TCAs *(10)*. Because of the low prevalence of TCA and PCP abuse and the high prevalence of diphenhydramine use in the general population, these tests often have low positive predictive values.

Recommendation. Stat testing for the following drugs is not recommended for ED patients presenting with acute symptoms: tetrahydrocannabinol (THC; marijuana), LSD, methaqualone, ibuprofen, and cotinine (nicotine metabolite). Testing for some other drugs, such as amphetamines, PCP, and propoxyphene, should be conducted in areas where these drugs exhibit notable prevalence. *Degree of consensus: B*

Discussion. The prevalence of methaqualone abuse is very low in the US today *(11)*. The number of ED visits resulting from PCP use exhibit marked geographic variation, but the total number is relatively low *(12)*. Although THC and LSD are more widely abused, many clinical toxicologists do not want or need to know whether a patient is positive for these drugs because they do not contribute to major acute clinical problems *(13)*. THC testing may be useful in drug compliance and rehabilitation programs that are outside the usual objectives of ED testing. Of course, testing for some of these agents (e.g., PCP and THC) may well be indicated in the evaluation of a child with altered mental status, where intoxication may be difficult to discern by history alone.

E. DRUG PANELS BY "TOXIDROMES"

Introduction. Patients who are drug intoxicated or overdosed often present to the ED with a collection of physical findings and symptoms that are consistent with a particular drug or class of agents. Recognition of these "toxidromes" can be important in the effective clinical management of ED patients *(14)*. Proper identification of a particular toxidrome could be used to exclude some drug

classes as the cause of the symptoms without urine drug testing. Drug testing panels can be established that link specific symptoms to a particular menu of tests: e.g., sympathetics (cocaine and amphetamines), sedatives (benzodiazepines, tranquilizers, and barbiturates), and hallucinogenic agents (THC, LSD, and PCP). Although implementation of such an approach could reduce unnecessary utilization of laboratory tests, the opportunity to identify the causative agent could be missed if the initial clinical impressions were wrong.

Recommendation. Clinical laboratories should not set up specific drug testing panels based on toxidromes. The failure to recognize a particular toxidrome may lead to the failure to order an important drug test. *Degree of consensus: A*

Discussion. Although clinical laboratories are under tremendous pressure to reduce costs and utilization of laboratory services, in cases in which urine has been collected and sent to the laboratory, elimination of a few drug tests that are available (i.e., regularly calibrated and quality controlled) as part of the test menus on automated testing platforms will not greatly impact the cost of delivering laboratory services. On the other hand, a delay in the triage and management of the overdosed patient because of inappropriate laboratory orders can greatly affect the cost for treating that patient and may have an adverse effect on patient outcomes. There has been at least one study that examined the potential success of linking toxidromes to particular ED drug-screening patterns *(15)*. When ED nurses, clinical pharmacists, and medical residents were asked to choose among eight toxidromes, the diagnostic accuracy was 79–88%, with the medical residents scoring the lowest of the group. Although these results indicate a reasonable degree of performance, the critical question is the clinical and fiscal impact for the 12–21% of patients incorrectly diagnosed, if the toxicologic causes of these cases were not identified. Inaccuracies in the assessment of toxidromes may be attributable to the presence of polydrug overdoses, delayed-onset toxicities *(16)*, or clinical inexperience. The importance of clinical experience in the ED is a major factor in the success of toxidrome accuracy and the potential use of specific drug panels. In a study of periodicity of drug overdose presentations, Raymond et al. *(17)* concluded that EDs are most likely to encounter overdosed patients in the early evening. This is also a time of peak activity in the ED, when problems with resident supervision, thoroughness of evaluation, and delays in patient management may be critical.

f. gastric samples

Introduction. Gastric contents can be sent to the laboratory for identification of orally ingested drugs. Gastric lavage is used on rare occasions to remove unabsorbed toxic substances. Administration of activated charcoal has become the treatment of choice for decontamination of toxins and poisons, with decreased utilization of gastric lavage *(18, 19)*.

Recommendation. There is no role for the testing of gastric contents in clinical management, although premortem collection and specimen retention may be important for cases with medico-legal considerations. *Degree of consensus: A*

Discussion. Although the analysis of gastric contents for drugs provides verification of what was consumed, unabsorbed substances do not contribute to the clinical presentation, and test results would not supercede toxicology data obtained on blood and urine. ED physicians must provide supportive care on the basis of existing signs and symptoms in the event that this information can be useful in analyses for forensic purposes, such as postmortem investigations.

g. "chain-of-custody" for clinical specimens

Introduction. Chain-of-custody documentation is a basic tenet of forensic and workplace drug testing. When a specimen is handled under chain-of-custody conditions, each individual who handles the specimen must sign a form that indicates when that specimen was in that individual's possession and when it was transferred to the next individual involved with the processing of that specimen. If the sample is to be stored for any reason, it must be in a secure and locked location, with limited access by only qualified personnel.

Recommendation. Maintenance of chain-of-custody documentation is unnecessary for samples collected for clinical toxicology purposes, and such practice should be discouraged. As with any laboratory specimen, proper procedures for collection, transport, results reporting, and storage are necessary. *Degree of consensus: A*

Discussion. In contrast to workplace drug testing, the principal aim of drug testing for hospitalized patients should be for diagnostic and treatment purposes. It therefore is unnecessary for the ED and the clinical laboratory to maintain a chain of custody for all urine specimens that are tested for drugs of abuse. Although results of laboratory tests may be introduced into court proceedings, this is an insufficient reason to require such documentation. The process is time-consuming, burdensome, and expensive; does not contribute to and may delay patient care; and should be discouraged. If it is known in advance that a specimen will likely be involved in a medico-legal matter, chain-of-custody procedures may be warranted and the ED staff should seek the assistance of qualified members of the laboratory staff.

Part II. Recommendations on Analytical and Reporting Issues for Drugs-of-Abuse Testing by Immunoassays

A. IMMUNOASSAYS

Introduction. Immunoassays, which have become the mainstay of stat urine drug testing, have major limitations in sensitivity and specificity. Many ED physicians are unaware of these limitations and will order all available immunoassay tests for every patient suspected of drug use, irrespective of the presenting signs and symptoms, lack of clinical significance for some drugs, availability of management measures, and local prevalence of use and abuse of that drug. Given the cross-reactivities demonstrated for many of these drug assays, the accuracy of testing for a drug with a low prevalence can be very poor. The limited number of available immunoassays for certain drug classes also limits the utility of this approach. Furthermore, many clinicians are not aware of what their own laboratory drug panel might cover *(20)*.

Recommendation. Optimum use of urine drug testing assays for ED patients requires an understanding of the limitations of existing commercial immunoassays for drugs of abuse. A close relationship between the clinical laboratory and ED staffs is necessary. The laboratory should clearly communicate to the ED staff the extent of the toxicology services available to them, such as the menu, target TATs, cross-reactivity data, and contact information for consultations. *Degree of consensus: A*

Discussion. The Committee feels that it is the joint responsibility of the ED and clinical laboratories to provide initial and continuing education on the limitations of drug testing to new house officers and to maintain a continuous medical education program for existing practitioners. It is also the responsibility of the in vitro diagnostics industry and, in some cases, the Food and Drug Administration (FDA) to alert the laboratory when changes to assays are made that could affect the performance and interpretation of urine drug testing results. It is clear that this knowledge is not adequately taught in medical schools, and it is inappropriate to expect that senior residents or attending staff will have sufficient understanding of these limitations to effectively educate their junior house staff. The laboratory must inform the ED staff when there are changes concerning the specificity and performance of commercial drugs-of-abuse immunoassays. They should also discuss the availability of new drug assays or assay platforms (e.g., POC testing devices) and the appropriateness of implementing such assays in that institution. On the other hand, ED physicians must inform the laboratory staff of changing drug utilization patterns; the appearance of new drugs or analogs, such as designer drugs *(21, 22)*; or testing and reporting needs that are not currently being met.

B. LISTING OF CROSS-REACTING SUBSTANCES ON IMMUNOASSAYS

Introduction. As described in the previous section, current immunoassays have considerable specificity limitations with respect to other compounds that are not members of the particular drug class being tested. In addition to direct educational activities, the laboratory should also document these specificity limitations when reporting results.

Recommendation. When immunoassays are used, the laboratory should list the major cross-reacting substances for each drug class when a positive result is reported. It may also be appropriate to indicate in a final report (e.g., in the "notes" section) that a negative urine drug result does not indicate absence of all drugs of abuse. *Degree of consensus: A*

Discussion. The issue of cross-reactivity for immunoassays is further complicated by the fact that there is heterogeneity in methodologies and formulations among assay manufacturers. The laboratory is directed to the package insert for specific cross-reactivity data and any changes in antibody cross-reactivity that might have occurred because of differences between reagent lots. The laboratory should compile an abbreviated list of major cross-reacting substances and make them available to the ED staff. Laboratory personnel should also be aware of additional data reported in the literature after the production of the assay and package insert or on new drugs marketed after the initial cross-reactivity testing was conducted. For example, oxaprozin, which was approved by the FDA in 1993, unexpectedly produced interference in most of the commercial immunoassays for benzodiazepines *(23)*. Validation studies are necessary if the laboratory modifies these assays to suit its needs (e.g., diluting the reagent to reduce costs). When in vitro interference studies are conducted, inclusion of drug metabolites is equally important to testing of parent compounds. Because it may be difficult to obtain supplies of the important metabolites, the use of urine from patients given the drugs to be tested is an alternative.

Given the importance of cross-reactivities to clinical practice, it was suggested during the open presentation of these guidelines that data be made available by manufacturers on their internet sites. It may be useful for clinical laboratories to note the manufacturer of the specific drug assay used in the final report, so that users of this information might know where to search for cross-reactivity data.

Another issue that was discussed in open sessions was how cross-reactivity data should be generated and listed in manufacturers' package inserts and on their web sites. Tests of potential interferents should be conducted at multiple concentrations because the cross-reactivity effects do not produce a parallel response. The concentrations tested should bracket the concentrations seen in routine therapeutic use and under toxic conditions. Stud-

ies of potentially interfering compounds should be conducted in both the presence and absence of the target analyte because the interferent can suppress the signal of the analyte, producing false-negative results *(24)*. The combining of different interferents within the same sample, as a means to reduce the amount of work necessary to generate interference data, should not be done because of potential drug–drug interactions. The data should be expressed as a percentage of interference. Methods for calculating cross-reactivities for immunoassays have been published previously *(25)*. After consultation with these investigators, the Committee recommends the use of the 50% displacement method for homogeneous nonisotopic competitive immunoassays.

Given the heterogeneity of approaches toward conducting and presenting cross-reactivity data, the Committee feels that a standardized approach would be in the best interests of the industry. This issue extends beyond the toxicology community and branches into all aspects of immunoassay testing; thus, it is beyond the scope of this work. It is unlikely, however, that the in vitro diagnostics companies will organize a committee with such an agenda. Establishing guidelines for cross-reactivity documentation could be a topic for a future AACC or NACB committee.

c. immunoassay cutoffs

Introduction. Qualitative assays for drugs-of-abuse testing require cutoff concentrations to distinguish between positive and negative results. Cutoffs are set on the basis of signal-to-noise ratio considerations, which are dependent on the precision, analytical sensitivity, and specificity of the assay. To reduce the number of false-positive results, the cutoff is set at a concentration that is higher than the assay limit of detection. As a consequence, there are urine samples that contain the target drug that are reported as negative because they are below the "administrative" cutoff concentration. The precision of automated immunoassay analyzers enables the use of lower cutoff concentrations without sacrificing specificity.

Recommendation. Cutoff concentrations optimized for workplace drug testing are not necessarily appropriate for clinical toxicology. Although a true-positive result indicates use, it does not presume impairment or intoxication of the patient at the time of specimen collection. *Degree of consensus: A.*

Discussion. The Substance Abuse and Mental Health Services Administration recently raised the workplace drug testing opiate cutoff from 300 to 2000 μg/L to reduce the number of opiate-positive results attributable to poppy seed consumption *(26)*. This reduced the frequency of false-positive indications of drug abuse. Although raising the opiate cutoff concentration may be appropriate for workplace testing, for clinical toxicology, the lower opiate cutoff concentration may be more desirable because the objective is to determine whether any opiates are present that may contribute to the clinical presentation or suggest the need for substance abuse counseling. The cutoff concentrations for other drugs should also be reviewed for appropriateness. For example, the cutoff for cocaine metabolites is set at 300 μg/L for workplace drug testing. Because of the cardiotoxic effects of cocaine, a lower cutoff, e.g., 100 μg/L, may be appropriate for ED patients and will increase the reported prevalence of cocaine use *(27)*. Lowering the cutoff concentration will also increase the number of cases of incidental drug-positive findings, i.e., those that do not contribute to the clinical symptoms of the patient. Manufacturers can assist laboratorians in designing or modifying assays that enable the use of more ideal drug cutoff concentrations.

d. inadequate spectrum of benzodiazepine detection by immunoassays

Introduction. Traditionally, antibodies used in immunoassays for benzodiazepines were directed against either the parent compound or an unconjugated form of a metabolite (such as oxazepam). For many benzodiazepines, however, this is inappropriate because the parent compound is not excreted into urine in high concentrations and the metabolites are in the conjugated forms. Furthermore, since the development of these assays, many additional benzodiazepines have been approved for use that do not metabolize to oxazepam. If the degree of cross-reactivity is low, these drugs have the potential to produce a false-negative result for the benzodiazepine class, even at higher concentrations than are typically seen in an overdose.

Recommendation. Some immunoassays for testing benzodiazepines are inadequate. Antibodies in optimum assays should be targeted toward the parent compound and principal conjugated metabolites or should utilize an online hydrolysis procedure to convert the conjugated metabolites to the unconjugated forms. *Degree of consensus: A*

Recommendation. Antibodies for benzodiazepines should be updated to identify the newer drugs in this class as they become approved and available for clinical use. *Degree of consensus: A*

Discussion. Immunoassays that are not sensitive to conjugated metabolites of all benzodiazepines on the market will produce false-negative results. Many investigators have shown that this problem can be overcome by treating the sample with a β-glucuronidase before immunoassay screening *(28)*. Although this step improves the usefulness of the assays, it is time-consuming and not practical for emergency (stat) testing. Some manufacturers have reformulated their benzodiazepine assays to incorporate an online hydrolysis step *(29, 30)*. Others have directed their antibodies toward conjugated metab-

olites *(31)*. The Committee feels that either of these approaches substantially improves the detection of benzodiazepines in urine. The Committee recognizes that updating immunoassays to include new drugs will be costly and time-consuming. One participant felt that lowering the benzodiazepine cutoff concentration to 50 μg/L in urine or adapting urine assays for use in serum or plasma was useful in improving the sensitivities of the assays.

E. Opiate vs Opioid Detection by Immunoassay

Introduction. The immunoassay for opiates is a source of much confusion because there is an expectation by many physicians that this assay will detect any opioid compound. Most commercial immunoassays, however, are directed toward free morphine and have various degrees of cross-reactivity toward codeine, 6-monoacetylmorphine, oxycodone, and hydromorphone and conjugated metabolites of these drugs. Current assays do not detect any of the synthetic opioids.

Recommendation. Immunoassays should detect most opioids (e.g., oxycodone, hydromorphone, meperidine, tramadol, buprenorphine, propoxyphene, and pentacozine) and not just codeine and morphine. *Degree of consensus: B*

Discussion. The opioid class of drugs can contribute to significant toxicities and clinical problems; however, a urine drug screen for "opiates" will usually produce a falsely negative result. Separate immunoassays are available for some of these opioids. The assay for methadone as an independent test is justified because of its specific use for the large number of methadone clinics worldwide. Individual assays for the other opioids may not be financially justified because of the lower prevalence of abuse of these agents. ELISAs for hydromorphone and other semisynthetic opiates are available for veterinary and dog- and horse-racing drug-testing laboratories *(32)* but are not adaptable to automated chemistry analyzers. Thus, the development of a "cocktailed" assay may be warranted in which a mixture of antibodies is added to detect the presence of these opioids. It is the opinion of the Committee that if such an assay were developed, it would be useful in ED settings. From the acute care viewpoint, however, the clinical response to an appropriate dosage and duration of therapy with naloxone in suspected opioid cases is a sufficient "diagnostic test", obviating the need for a positive urine test. In addition, problems with the specificity of the opiate assay have been identified, with cross-reactivities with such entities as the quinolone antibiotics *(33)*.

F. Immunoassays for Amphetamines vs Sympathomimetic Drug Class

Introduction. The term "amphetamines" has been inappropriately applied to a family of amines that have stimulant and sympathomimetic properties. Drugs in the former category include D-isomers of amphetamine, methamphetamine, phentermine, and the designer amines, methylenedioxyamphetamine and methylenedioxymethamphetamine. They are used as appetite suppressants and are abused as recreational drugs *(34)*. The sympathomimetic amines are present in nonprescription cold medications, such as decongestants, and in diet pills. Some of these include ephedrine, pseudoephedrine, phenylpropanolamine (recently removed from the US market), and phenylephrine. These over-the-counter sympathomimetic amines are abused and can produce significant toxicity. For workplace drug testing, highly selective immunoassays have been developed that use monoclonal antibodies targeted toward detection of the illicit amphetamine and methamphetamine *(35)*. Other immunoassays that use polyclonal antibodies are also available that are able to detect both illicit and sympathomimetic amines *(36)*. Tests for all of these drugs may be important in the ED evaluation of a patient with agitation or "sympathetic" toxidrome.

Recommendation. The optimum immunoassays to test for amphetamines in ED patients are those directed toward a broad spectrum of amines as a class, rather than assays that are directed specifically toward the illicit amines. An assay directed toward phenylethyl amines would largely cover this class. The name of the test should be changed from "amphetamines" to "sympathomimetic amines" or "stimulant amines". *Degree of consensus: A*

Discussion. Some manufacturers of immunoassays offer two amphetamine assays. In this case, the laboratory should select the more nonspecific sympathomimetic amine assay for ED practice and reserve the monoclonal amphetamine assay for specific detection of the illicit drugs. For manufacturers who offer only the monoclonal assay for the illicit amphetamines, laboratory personnel should communicate the sensitivity limitations of this assay to the ED staff. Manufacturers are urged to provide a broad-spectrum "amine" assay for testing on automated chemistry analyzers should such an assay not be available.

G. Confirmation of Positive Immunoassays

Introduction. A basic tenet for forensic drug testing analysis is the use of two analytical methods that differ from one another in the basic chemical principles *(37, 38)*. GC/MS is the definitive and defensible method for analysis for drugs of abuse. Given the difficulties and expense of performing GC/MS in real time, the need for obtaining stat results negates the value of confirmation analysis in ED cases. If the clinician anticipates subsequent involvement with medico-legal or social services or there is a clinical need to identify the specific drug yielding a positive immunoassay result, the staff should notify the laboratory of the need for a confirmative analysis.

Recommendation. When reporting results of immunoassay screening, there must be proper notation given that the assay used is considered as a "screening test" and that any positive results are to be considered as "presumptive". *Degree of consensus: A*

Recommendation. The laboratory should not routinely perform confirmative analyses on positive screening results. *Degree of consensus: A*

Recommendation. When confirmation is needed, the laboratory should store these specimens for an indefinite period or until the case is resolved. The laboratory should consult with the hospital's risk management department for further guidance. *Degree of consensus: B*

Discussion. The standards for forensic toxicology are different from those for clinical toxicology, and the results of unconfirmed urine drug testing should be used only as a single data point to assist patient management decisions. The costs of providing GC/MS analysis on a stat basis are prohibitive for all but the most specialized of academic centers. The TAT for typical GC/MS confirmation is long (>4 h) and likely to be unacceptable for real-time use by ED physicians. Nevertheless, laboratory tests can be entered into court proceedings, and there can be inappropriate interpretations made because of the inaccuracies of immunoassays. Confirmation may be necessary if there is anticipated involvement of medico-legal or social services. Because these situations will be unknown to the laboratory, appropriate communication is required from the clinical service. In the absence of confirmative testing, the limitations of immunoassays and their effect on the interpretation of drug testing results will need to be presented and argued in court proceedings. As a compromise, it may be useful for a laboratory to store positive urine drug screen results for a period of time, e.g., 3 months to 1 year, to enable confirmative testing of challenged cases at a later date. The ED staff should be notified as to the policy for toxicology specimen retention. This may not be ideal, however, because some cases do not surface for many years after an ED episode, and adequate storage space is likely to always be an issue.

Part III. Recommendations for Specific Analysis of Ethyl Alcohol and Other Toxic Alcohols

Introduction. The measurement of alcohol in body fluids and/or breath is an important test in the management of patients who present to the ED. A given ethanol concentration is difficult to interpret because clinical symptoms do not correlate well with any given serum or plasma concentration because of individual tolerance and possible co-ingestion or coexisting conditions. Nonetheless, an abnormally high result may be helpful in determining the cause of presenting signs and symptoms. A negative alcohol result may be even more important to the ED staff because it directs their attention toward other possible etiologies and diagnostic procedures. Ethanol is also used as a therapeutic drug for patients with toxic alcohol intoxications and for ethanol withdrawal syndrome. When ethanol is in use, frequent determinations are needed to ensure adequate dosing.

Although the whole-blood alcohol concentration is important from a law enforcement viewpoint, e.g., the determination of driving under the influence, forensic cutoffs (e.g., 0.08% or 0.1%) have no relevance from a clinical management viewpoint because there is no concentration that consistently defines clinical intoxication. This justifies the use of samples other than whole blood, including serum or plasma, saliva, and breath. Although there are subtle differences in results among these specimens, the magnitude of these differences, i.e., 10–20%, are also without clinical significance. Therefore, a laboratory or ED has choices regarding the optimum specimens and testing methods that best meet its clinical needs. As such, many hospitals have implemented alternative samples for alcohol testing because of their low cost and convenience.

a. need for a breath alcohol quality-assurance/quality-control program

Introduction. Portable and bench-top breath alcohol devices have been available for many years and are widely used for traffic law enforcement. Current alcohol breath analyzers are accurate, precise, and inexpensive. As a result, many EDs have adopted breath meters for determining bedside alcohol concentrations in intoxicated patients. Currently, the Clinical Laboratory Improvement Act of 1988 does not regulate breath alcohol testing because a discrete sample is not collected and analyzed separately (the exhalation of breath directly into a device does not constitute sample collection). Thus, in the manner that a pulse oximeter measurement is not subject to these regulations, neither is breath alcohol measurement. Nevertheless, because of the importance of alcohol measurement, the Committee feels that laboratory oversight is necessary. The recommendations that follow were formulated by a Task Force of the AACC Therapeutic Drug Monitoring and Clinical Toxicology Division *(39)*.[12] The Task Force does not necessarily endorse the substitution of breath alcohol measurements for the serum or plasma alcohol test.

Recommendation. Clinical breath alcohol testing is POC testing and must meet the same quality-assurance (QA)/quality-control (QC) requirements as any POC test. As a part of the laboratory's ongoing QA effort, a program must be in place to monitor and evaluate policy, proto-

[12] The recommendations for breath alcohol testing were generated by a task force of the Toxicology and Therapeutic Drug Monitoring Section of the AACC. Members of this committee included Tai C. Kwong (chair); Richard W. Jenny, Department of Health, State of New York; Saeed A. Jortani, University of Louisville (Louisville, KY); and Richard D. Pinder, Department of Public Health, State of Connecticut.

cols, and the total testing process so that breath alcohol results are accurate and reliable. The clinical laboratory should be involved in the design, implementation, and monitoring of the quality assurance program. *Degree of consensus: A*

Discussion. Elements of an effective QA program include monitoring and evaluating the overall quality of the total testing process (preanalytic, analytic, and postanalytic steps) as well as the evaluation of effectiveness of policies and procedures; identification and correction of problems; assurance of accurate, reliable, and prompt reporting of test results; and affirmation of the competency of operators. It is necessary to have a comprehensive up-to-date accessible Standard Operating Procedure manual, operator training and evaluation of competency, and a QC program. Each device must be checked for accuracy each day by use of a dry gas standard and an air blank. The recovery of alcohol must be within the tolerance established by the manufacturer. The essential operator procedures are listed in Table 4.

B. Selection and Validations of Breath Alcohol Devices

Introduction. Given that breath alcohol analyzers are POC testing devices, the same requirements, principles, and responsibilities that govern POC tests should also be applicable. Clinical laboratory personnel are the most experienced, trained, and qualified to evaluate analytical performance such as precision, accuracy, reliability, sensitivity, and specificity.

Recommendation. The laboratory should be involved in the selection, validation, and deployment of the breath alcohol devices used. *Degree of consensus: A*

Discussion. The selection of breath alcohol devices should be based on performance and features that meet the requirements of clinical services. Only devices listed in the National Highway Traffic Safety Administration Conforming Product List should be used *(40)*. Table 5 lists the Committee's recommendation for specific device specifications and desirable attributes for breath alcohol measurements in the ED.

The clinical laboratory has the responsibility to validate that the device performance meets or exceeds specifications before release of the technology for clinical use at near-patient sites. This includes familiarization with the technology by use of vendor-supplied educational materials or programs and adjustment of manufacturer's guidance to clinical service requirements. Verification of device performance characteristics requires use of a National Highway Traffic Safety Administration-approved breath alcohol simulator and certified alcohol solutions or certified dry gas alcohol standards. The analytical performance should be evaluated against experimental protocols established by the NCCLS *(41)*. The accuracy and precision studies should be performed at clinically relevant alcohol concentrations. The specificity should be challenged with aqueous solutions of volatiles (acetone, methanol, isopropanol) at concentrations likely to be encountered in clinical settings. The calibration stability should be verified with suitable QC materials on each day that the device is used.

C. Reporting Units for Ethyl Alcohol

Introduction. Over the years, the reporting of ethanol testing has been the source of much confusion between individuals in the healthcare field and those who use alcohol results for forensic purposes. In most states, the accepted limit for alcohol is typically 1.0 g/L (0.10 g/dL) in whole blood. Some clinical laboratories measure alcohol concentrations in serum or plasma and report values in milligrams per 100 milliliters (mg/dL). Because ethanol is very water soluble, its distribution in various body fluids is dependent on the water content of those fluids *(42)*. The water content for serum or plasma is typically 98%, whereas for whole blood, the water content is ~86%

Table 4. Essential operator procedures for breath alcohol analysis.

- Use of test device under manufacturer-recommended environmental conditions
- Use of a properly calibrated device
- Verification that the blank and alcohol accuracy (QC) recoveries are within specifications
- Use of an air check or blank breath test immediately before the patient test
- Confirmation of patient identification
- Examination of the patient to ascertain that residual alcohol and foreign objects are cleared from the mouth
- Instruction of patient on proper delivery of a deep-lung sample
- Documentation of test date, time, device, QC result, patient identification, and results
- Prompt and accurate reporting of results.

Table 5. Device specifications and desirable attributes for POC breath alcohol analysis.

Device specifications

- Accuracy and precision should meet or exceed performance required for intended clinical use
- Prevents false-positive results from acetone (up to 0.2 g/L)
- Clinically appropriate analytical (reportable range in units of g of alcohol/100 mL of blood)
- Environmental conditions appropriate for operation

Desirable attributes

- Mistake-proof for ease of use by nonlaboratory personnel
- Procedural controls that monitor requisite operator steps and specimen delivery
- Function checks that monitor components performance
- Data logging capability
- Printer and/or laboratory information management system interface
- Battery-operated devices should have a "low battery" indicator

(with a normal hematocrit). Therefore, whole-blood alcohol concentrations are lower than serum or plasma values. However, a constant conversion factor cannot be applied because the hematocrit can dramatically change from individual to individual. It should be noted that these legal definitions have little or no clinical meaning in the ED.

Recommendation. Alcohol concentrations should be reported in units clearly defined by the laboratory, with a notation as to the sample matrix that was tested (serum or plasma, urine, whole blood, breath) and methodology. *Degree of consensus: A*

Discussion. A wide variety of technologies are available to quantify alcohol in biological fluids. The laboratory, with advice from the ED, should clearly identify the type of technology used, the specimen of choice, and the reporting units. The vast majority of clinical alcohol assays are based on the alcohol dehydrogenase enzymatic assay of serum or plasma. An absolute conversion of serum or plasma alcohol concentration to whole-blood alcohol concentration should not be made.

There was some discussion on the applicable reporting units for breath alcohol. It is most scientifically correct to express the breath concentration per 210 L of expired air. Use of this unit will also make it more obvious that a breath sample was tested. Most physicians, however, are unfamiliar with the subtle differences between mg/210 L (breath) and mg/dL (blood) and are likely to remember only the actual number. The Committee has decided to keep the mg/dL designation because these are the units used in law enforcement applications where breath alcohol testing is most frequently used. Some countries report in units of mmol/L. These units can be directly used in osmolality calculations.

Other types of samples, such as saliva and sweat, have been used for workplace drug testing applications. For clinical toxicology, the Committee felt that there is insufficient experience or peer-reviewed evidence in a clinical setting to render a recommendation regarding these matrices at this time.

D. ASSAYS FOR METHANOL AND ETHYLENE GLYCOL

Introduction. Methanol and ethylene glycol are substances that are not toxic by themselves but that produce metabolites that cause significant morbidity and mortality. Methanol metabolizes to formaldehyde and then to formic acid, which produces a significant metabolic acidosis *(43)*. Ethylene glycol breaks down to oxalic and to a greater extent, glycolic acids, which contribute to a significant metabolic acidosis *(44)*. These metabolites also contribute to significant renal tubular necrosis. Porter *(45)* recently showed that all patients with a glycolic acid concentration >10 mmol/L developed acute renal failure. Detection of these intoxicants in blood may be important for therapeutic management if a more convenient assay for this metabolite can be constructed. A new antidote, fomepizole (Antizol), a competitive inhibitor of alcohol dehydrogenase (enzyme responsible for the initial step in both methanol and ethylene glycol conversion), is FDA-approved for the treatment of ethylene glycol *(46)* and methanol poisoning *(47)*. Hemodialysis also may be indicated at concentrations >250–500 mg/L (25–50 mg/dL), even in the absence of a metabolic acidosis, which may be delayed in its presentation.

Direct laboratory tests for methanol and ethylene glycol are needed because toxicities can occur without clinical signs of inebriation. Because these tests are not available in many medical centers, surrogate markers, particularly for ethylene glycol exposure, have been proposed. These include examination of urine for the presence of dihydrate calcium oxalate crystals and checking for urine fluorescence attributable to the presence of fluorescein added to some commercial antifreeze products. Both of these surrogate markers suffer from false-positive and -negative findings. Rhomboid oxalate crystals are found in only ~33–50% of known ethylene glycol cases, whereas urine fluorescence is observed only within the first few hours of ingestion and only with antifreeze products that contain the dye *(48, 49)*.

Recommendation. Clinical laboratories should provide direct measurements for methanol and ethylene glycol in serum or plasma. If GC, the assay should target glycolic acid, the toxic metabolite, in addition to the parent intoxicant, ethylene glycol. *Degree of consensus: B*

Discussion. The most definitive method for methanol and ethylene glycol is GC. Although this methodology is not widely available in most clinical laboratories, the Committee recommends its use for delivering stat results. However, enzymatic procedures for methanol and ethylene glycol are available that can be adapted to chemistry analyzers that are "open" (i.e., where nonvendor or "homebrew" reagents are prepared and assayed on the instrument). Because of the low volume of testing for these analytes, there are no prepackaged commercial reagents for these tests. In the assay described by Vinet *(50)*, methanol is converted to formaldehyde and formic acid by alcohol oxidase and formaldehyde dehydrogenase. In the modified assay described by Ochs et al. *(51)*, ethylene glycol reacts with glycerol dehydrogenase to produce hydroxyacetaldehyde. This assay requires removal of endogenous triglycerides by the addition of lipase to the reagent. Because the endogenous triglyceride concentration constitutes the blank and must be subtracted from the signal, high triglycerides can increase the imprecision of the ethylene glycol measurement. High concentrations of lactate dehydrogenase and lactic acid interfere with this assay, producing false-positive results *(52, 53)*. A microdiffusion procedure for methanol and ethylene glycol in serum or plasma has also been developed *(54)*.

This recommendation provides the clinical justification to encourage in vitro diagnostics manufacturers to develop rapid and more specific assays for methanol and ethylene glycol for use on automated clinical chemistry analyzers. Fig. 1 illustrates the history of one hospital, which initially imposed restrictions (such as requiring surrogate testing and discussion with a clinical toxicologist) before approval of testing for methanol and ethylene glycol. When these roadblocks were removed, the volume for these tests, which are based on enzymatic procedures, increased substantially. This experience suggests that even if the prevalence of toxic alcohol ingestion for a given geographic location is low, requests for these tests can be substantial because symptoms and signs consistent with toxic alcohol ingestion are frequently attributable to other clinical conditions.

E. OSMOLALITY MEASUREMENTS FOR TOXIC ALCOHOL SURVEILLANCE

Introduction. The Committee recognizes that many laboratories may not have instruments with which noncommercial reagents can be used or that laboratories may not have the capability to prepare and validate homemade reagents. Other surrogate markers, e.g., measurement of the serum or plasma osmolality and calculation of the osmolal gap, have been studied as alternatives to direct assays of these alcohols *(55, 56)*. The osmolality of a fluid is defined as the moles of solute dissolved in a kilogram of solvent. Osmolality is typically measured by the freezing point depression method and has a serum or plasma reference interval of 275–295 mOsm/kg. In normal serum or plasma, the major contributing components are the monovalent electrolytes, glucose, and blood urea nitrogen. The calculated osmolality is based on the contributions of these components, and the gap is the difference between measured and calculated:

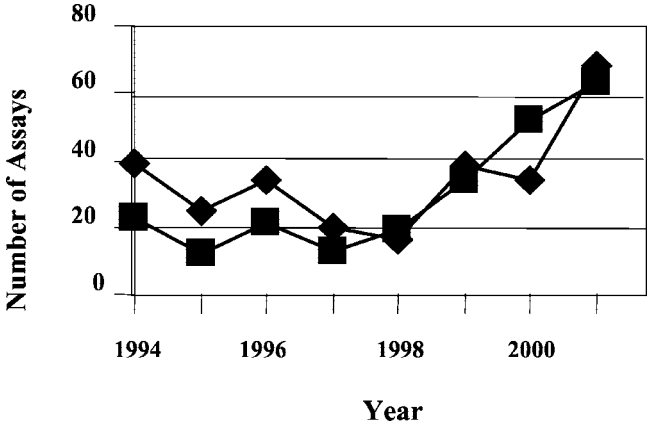

Fig. 1. Increasing utilization of alcohol toxicity assays vs laboratory testing policy at Hartford Hospital.

In 1994, chromatographic testing required approval by the toxicologist on call. In 1996, the enzymatic assays for methanol (■) and ethylene glycol (♦) were introduced. In 1998, the consult approval requirement was waived. Although the incidence of positive results has not increased during this period (typically 3–5 patients/year), these steps have led to substantially increased test utilization.

$$1.86(Na^+, \text{mmol/L}) + (\text{glucose, mg/dL} \div 18) + (\text{blood urea nitrogen, mg/dL} \div 2.8)$$

Many other formulas have been proposed for the calculation of osmolality *(55, 57)*, but none of them accounts for the presence of ethanol, a common finding in the ED population that is typically being tested. Note, however, that the 95% confidence interval for osmolal gap ranges from −14 to +10. The equation given above appears to produce a normal osmolal gap, i.e., close to zero, as do any of the formulas. The gap is increased in the presence of methyl and ethyl alcohols, acetone, ethylene glycol, mannitol, and other low-molecular-weight hydrocarbons, proportional to their millimolar concentration in blood. The higher glycol ethers have a minimal effect on the osmolal gap *(58)*. Measurements for ethanol are readily available and should be considered in cases where there is a substantial increase in the gap (e.g., >10 mOsm/kg).

Recommendation. Inherent problems with the measured osmolality and calculation of the osmolal gap reduce the reliability of these measurements in the differential diagnosis of volatile and ethylene glycol alcohol intoxication in patients. A very high osmolal gap (e.g., >50 mOsm/kg) requires investigation of a toxic alcohol or other agents that can increase the osmolality. *Degree of consensus: B*

Discussion. Although an increased gap in the presence of a metabolic acidosis suggests the presence of methanol or ethylene glycol, there are other conditions that are associated with an increased osmolal gap. In a patient with an established metabolic acidosis from toxic alcohol ingestion, a normal or low osmolal gap can occur if blood is sampled after the volatile alcohols have been converted to the acid metabolites *(59)*. Increases in the osmolal gap can occur in patients with multiple organ failure and other unmeasured osmolal entities *(60, 61)*, and can falsely suggest toxic alcohol exposure. A low osmolal gap is a poor discriminator as well. Although a markedly negative gap (e.g., less than −10 mOsm/kg) in a patient without metabolic acidosis essentially rules out recent toxic alcohol ingestion, this is a very rare finding.

F. ISOPROPYL ALCOHOL PROPYLENE GLYCOL INTOXICATION AND ACETOACETIC ACID

Introduction. Isopropyl alcohol, also termed "rubbing alcohol", is used as an antiseptic agent. It is not as toxic as methanol or ethylene glycol because this alcohol does not metabolize to an acid. Although there is wide availability of this alcohol in the US, its distribution is more limited in other countries. Intoxicated patients will present with some degree of central nervous system (CNS) depression, slurred speech, ataxia, and gastritis. Nevertheless, diagnosis of isopropyl alcohol abuse is important for patient management decisions. Serum or plasma isopropyl alco-

hol concentrations of 500 mg/L (50 mg/dL) are associated with signs of intoxication, and concentrations >1500 mg/L (150 mg/dL) are associated with coma *(62)*. The major metabolite of isopropyl alcohol is acetone. Although spot tests are available for the determination of ketones in serum or plasma and urine, these tests have limitations in sensitivity and specificity.

Propylene glycol is found in activated charcoal products, as a diluent for several therapeutic drugs, and as an alternative to ethylene glycol in antifreeze. It can cause CNS toxicity, metabolic acidosis with increased lactate, and increased serum or plasma osmolality. In general, this alcohol usually appears as the cause of a mild metabolic acidosis and source of developing osmolal gap in the intensive care unit setting *(63, 64)*. Patients with propylene glycol exposure usually respond to supportive care and discontinuation of infusion of medications prepared with propylene glycol diluents.

Recommendation. Quantification of isopropyl alcohol and propylene glycol by GC is the preferred approach to their identification. Measurement of lactate is appropriate for monitoring patients exposed to propylene glycol because this is the major metabolite. *Degree of consensus: A*

Recommendation. Because propylene glycol is used as a vehicle in some drug preparations and there can be inadvertent exposure, this alcohol should not be used as an internal standard for the GC analysis of volatile alcohols. *Degree of consensus: A*

Recommendation. In the absence of GC testing for isopropanol, the "Acetest" may be used as an insensitive surrogate because there is some reactivity of this reagent toward acetone. However, the name of the test should be listed as "acetoacetic acid" and not "ketones", "ketone bodies", or "acetone", as this test has the highest sensitivity toward acetoacetic acid. *Degree of consensus: A*

Discussion. Quantification of isopropyl alcohol by GC is the preferred test to identify exposure. However, it is recognized that many clinical laboratories do not have this technology. Where such technology is not available, identification of ketone bodies may be a useful alternative. Ketone bodies, e.g., acetoacetic acid, acetone, and β-hydroxybutyric acid, are derived from acetyl-CoA and are released into the blood and excreted into the urine after excess breakdown of β-fatty acids. The nitroprusside reaction for ketones, first described in 1883 *(65)*, is ~10-fold more sensitive for detecting the presence of acetoacetic acid than for acetone and has no reactivity toward β-hydroxybutyric acid. Typical detection limits for acetoacetic acid, which is not produced in isopropyl alcohol intoxication, are in the range of 50–100 mg/L (5–10 mg/dL). Because of the higher detection limit for acetone, false-negative results can occur in patients who have ingested small amounts of isopropyl alcohol. The nitroprusside test can also produce false-positive results in the presence of phenylketones, bromosulfophthalein, and sulfhydryls *(66)*.

Part IV. Recommendations on Laboratory Assays for Other Toxicants as Causes of Poisonings

A. "UNIVERSAL" ACETAMINOPHEN AND SALICYLATE SCREENING

Introduction. Acetaminophen overdose is a common clinical problem, with >111 000 exposures reported to US poison control centers and 40 000 associated ED cases per year. When ingested in therapeutic doses, the majority of acetaminophen is detoxified by conjugation and excreted in the urine. Ingestion of toxic amounts of acetaminophen causes more of the drug to be metabolized by the CYP2E1 isoenzyme of cytochrome P450 to *N*-acetyl-*p*-benzoquinone imine, a highly reactive intermediate *(67)*. Failure to detoxify or clear this metabolite leads to fulminant hepatic failure. Therapy with *N*-acetylcysteine is most effective when initiated within 8–12 h after ingestion. Unfortunately, the early stages of acetaminophen toxicity are usually asymptomatic or, when present, are nonspecific and can be easily missed *(68)*. Once the first signs of hepatic injury become apparent [e.g., right upper quadrant pain and tenderness, increases in the concentrations of serum or plasma aminotransferases, and prolonged prothrombin times (PTs)], treatment may be less effective. In those few patients who develop fulminant hepatic failure, orthotopic transplantation may be the only remaining therapeutic option.

Determination of a single serum or plasma acetaminophen concentration will confirm ingestion and, with the Rumack–Matthew nomogram, allows for the initiation of appropriate therapy *(69)*. In cases in which the time of ingestion is unknown, repeat testing over 2–4 h may be helpful to demonstrate completion of absorption after overdose. Serial testing on a 4- to 8-h basis may be used to estimate the elimination half-life. This may have some prognostic value when the time of ingestion in unknown *(70, 71)*. However, in most cases, it is unnecessary to monitor acetaminophen concentrations to document a decreasing concentration. The nomogram is not useful for overdose management of patients who present with chronic overuse of acetaminophen, i.e., consistently high therapeutic concentrations of acetaminophen.

In contrast to the situation with acetaminophen, salicylate overdoses are usually characterized by symptoms of tinnitus, tachypnea, and the findings of a mixed respiratory alkalosis and metabolic acidosis. It is rare to find a completely asymptomatic salicylate overdose; it is unlikely that specific treatment would be indicated for a mild overdose *(72)*. Patients with chronic salicylate ingestion can present with altered mental status alone, but are hardly asymptomatic.

Recommendation. All ED patients who present with intentional drug ingestion and chronic overuse secondary to

chronic pain should be screened with a quantitative serum or plasma acetaminophen assay. *Degree of consensus: A for quantitative serum or plasma screen.*

Recommendation. Screening for the presence of salicylate can be guided by clinical findings or acid–base abnormalities. *Degree of consensus: A*

Discussion. In the absence of specific symptoms to suggest the presence of a disorder, the introduction of a screening test for a particular population requires careful consideration before implementation. In the case of acetaminophen screening, the cost of testing many patients to identify a small number of acetaminophen-overdosed patients must be weighed against the cost of treating missed acetaminophen ingestions that progress to fulminant liver failure. The incidence of detectable acetaminophen in the blood of patients with suicidal intent or mental status changes is 6–11%. There have been a few studies conducted to determine the number of patients who deny ingestion of acetaminophen but have a potentially hepatotoxic acetaminophen concentration. In the study of Sporer and Khayam-Bashi *(72)*, only 5 of 1820 patients (0.3%) had a negative history and an acetaminophen concentration of >50 mg/L. On the other hand, Ashbourne et al. *(73)* found that 7 of 365 (1.9%) of patients had ingested acetaminophen at potentially toxic concentrations. The committee concluded from these studies that routine screening is warranted; however, there have been no outcomes studies to show that this approach is cost-effective or provides medical benefit. Nevertheless, the Committee felt that assessment of acetaminophen concentrations was appropriate given the considerable costs associated with even a single case of potentially preventable fulminant hepatic failure.

There was some discussion in the open forums about the usefulness of a qualitative assay in urine to screen for acetaminophen. The rationale is that if the results on the majority of samples tested are negative, the need and costs for performing quantitative serum or plasma testing would be diminished. Fig. 2 shows the distribution of serum or plasma acetaminophen concentrations at one hospital. In 84% of the tests, acetaminophen was undetectable, and the results were <50 mg/L in the majority of the cases (94%). If a urine assay were used, positive tests would require follow-up with a quantitative acetaminophen concentration in serum or plasma. An important aspect of developing such an assay would be determining the most appropriate cutoff that differentiates between therapeutic use and potentially toxic exposure. Such a cutoff would require validation in a clinical study that has yet to be conducted.

Contrary to the recommendation for acetaminophen screening, the Committee does not endorse routine screening for the presence of salicylates. The finding of an "unexpected" positive serum or plasma salicylate result is less frequent than for acetaminophen (0.16% vs 0.3%) *(72)*.

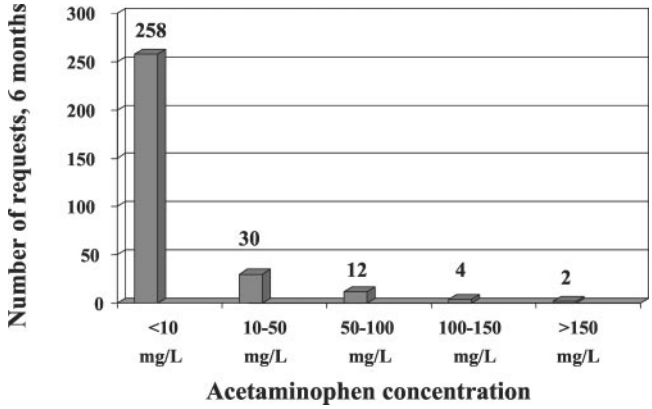

Fig. 2. Histogram of serum acetaminophen testing results at Hartford Hospital for 6 months.

Salicylate screening is a low-cost test that is warranted in patients with altered mental status. In an alert patient, the clinical findings of tinnitus, tachypnea, and the presence of a mixed respiratory alkalosis and metabolic acidosis should suggest the need for salicylate testing. These symptoms and signs may provide sufficient evidence of salicylate toxicity to begin treatment without a quantitative serum or plasma salicylate determination. Furthermore, a quantitative serum or plasma result has little bearing on prognosis compared with the clinical and acid–base presentation. Although important historically (representing the first recognition of the importance of time post-ingestion and its effect on plasma drug concentration), the Done nomogram *(74)* should never be used in isolation to assess toxicity or to guide therapy. Done's initial small retrospective study has not been prospectively validated *(75)*.

B. CYANIDE AND HYDROGEN SULFIDE

Introduction. Cyanide and hydrogen sulfide are chemical asphyxiants that disrupt cellular oxidative phosphorylation. These toxic gases are often produced as byproducts of industry and combustion. Patients exposed to low concentrations of cyanide have nonspecific symptoms of nausea, vomiting, abdominal pain, and upper gastrointestinal irritation, with higher concentrations or prolonged exposure causing cardiac and CNS dysfunction and death *(76)*.

Recommendation. The ED must rely on history and physical examination to determine whether treatment with cyanide antidote is appropriate. Collection of a blood sample for later cyanide and sulfide testing may be useful to document exposure. *Degree of consensus: A*

Discussion. Although rapid experimental assays have been developed *(77)*, they have not been tested or implemented in an ED setting. In the case of cyanide and sulfide exposure, immediate application of the antidote is indicated (e.g., nitrites) if the patient has a history of possible

exposure and rapid onset of symptoms of hypoxemia (gasping), oxygenated venous blood (indicating absence of oxygen extraction by the tissues), wide anion gap, and tachycardia; occasionally, the smell of bitter almonds on the patient's breath or clothing will indicate the presence of cyanide, whereas a rotten egg odor identifies hydrogen sulfide. Treatment must be started immediately if therapy is to be successful *(78)*. The ED cannot wait for the results of laboratory tests to confirm cyanide or sulfide exposure. However, it is useful to collect a blood sample for later testing to validate (or refute) exposure. It should be noted that some authors have suggested that cyanide and hydrogen sulfide are not stable in blood and that blood thus should be tested as soon as possible *(79)*.

A potential stat surrogate is the measurement and comparison of arterial and (mixed) venous blood gases. A narrow Po_2 difference suggests poor extraction of oxygen by the tissues and is consistent with the presence of a cellular asphyxiant *(80, 81)*.

c. anticoagulants

Introduction. Anticoagulants are used as rodenticides and act by inhibiting critical vitamin K-dependent coagulation factors, especially factors II, VII, IX, and X and proteins C and S, causing severe bleeding and eventual death. Most cases of rodenticide exposure do not require an ED visit as toxicity is uncommon with accidental ingestion. For patients who intentionally ingest rodenticides, the appropriate therapy is an infusion of fresh-frozen plasma and parenteral vitamin K_1 *(82)*. Patients with prolonged coagulation studies who respond to 2–3 days of vitamin K therapy and relapse should be evaluated for exposure of long-acting anticoagulants such as brodifacoum. The increased use of long-acting anticoagulants has led to more accidental and suicidal ingestions of these products. Most surveys indicate that accidental ingestion rarely leads to bleeding problems *(83)*, whereas suicidal ingestion often requires several months of vitamin K_1 therapy before the blockage of vitamin K_1 regeneration is resolved *(84, 85)*.

Recommendation. Patients who intentionally ingest anticoagulants, particularly the long-acting formulations, should be monitored for coagulation status by the prothrombin time (PT) test. Samples should be collected at 24–36 h after exposure to monitor anticoagulation effects without prophylactic vitamin K administration. There is no stat clinical need for determining the identity or concentration of the specific anticoagulant taken. *Degree of consensus: A*

Discussion. Follow-up for long-acting anticoagulant ingestion is not usually performed in the ED. Because the effect of the ingestion depends on both depletion of a functioning cofactor (vitamin K) and depletion of existing coagulation factors, testing should be done within 24–36 h. A baseline test is not usually necessary unless the time or chronicity of ingestion is unknown. In general, administration of vitamin K_1 should not be started until an increase in PT has been demonstrated, as this may delay recognition of a significant ingestion. Testing for factors V and VII may be useful in the workup of a bleeding patient to differentiate between hepatic factor insufficiencies and anticoagulant exposures. Specific concentrations of factor VII will also decrease hours before the PT is affected *(86)*; however, stat testing is unlikely to be available.

d. lead poisoning

Introduction. Lead can have serious consequences if a poisoning is left untreated. The Toxic Exposure Surveillance System documented 2918 exposures for the year 2000 *(4)*. Acute lead exposure produces gastrointestinal distress and encephalopathy at very high concentrations, whereas chronic exposure interferes with mental development, bone growth, and nerve function and causes anemia and nephropathy. Young children are particularly sensitive to the effects of lead. Guidelines *(86)* published by the US CDC in 1991 recommend screening of all children at the age of 2 years for low-level exposure because the prevalence of exposure in this group can be very high *(87)*. These guidelines have subsequently been amended to focus screening in areas of high environmental lead contamination *(88)*.

Recommendation. Emergency testing for lead is not required to support ED practice. The ED should be prepared to collect heparinized blood samples for lead testing when lead exposure is suspected; however, specific treatment is usually not initiated in the ED. Because lead is ubiquitous in the environment, needles and collection and transfer tubes need to be free of lead contamination ($\leq$5 μg/L). Next-day availability of the blood lead result is adequate to ensure appropriate follow-up. Collection of serum or plasma for lead evaluation is not appropriate. The erythrocyte protoporphyrin (EPP) test is not useful for detecting low-level exposure. *Degree of consensus: A*

Discussion. Whole-blood lead measurement has been identified by the CDC *(86)* as the best test to detect lead exposure. Whole-blood lead concentrations $<$100 μg/L (10 μg/dL) are considered normal in children. Higher values initiate a cascade of evaluation and potential treatment recommendations. Whole-blood lead concentrations $>$300 μg/L (30 μg/dL) in adults are indicative of significant exposure. Blood lead concentrations $>$600 μg/L (60 μg/dL) represent serious exposure requiring removal from the workplace and often treatment with chelation therapy.

The EPP test does not have sufficient sensitivity to detect low-level lead exposure, but it is a marker for overdose. An EPP concentration $>$600 μg/L (60 μg/dL) is a significant indicator of acute lead exposure. Serum or plasma lead analysis has no clinical utility in cases of acute lead exposure because concentrations are abnormal only for a short period of time after exposure. Measure-

ment of urine excretion rates either before or after chelation therapy has been used as an indicator of lead exposure, but this approach is not indicated in ED practice. Because the blood lead concentration has the strongest correlation with toxicity, this test is recommended for evaluation of lead exposure by the ED.

Some reviewers of this document have suggested that when specimens are collected for blood lead determinations, the same lot of empty containers should also be sent to the laboratory to determine the degree of lead contamination in the tubes, cups, or needles attributable to the manufacturing process. This will enable a more accurate determination of the lead concentration actually present in the blood sample.

e. testing for iron toxicity

Introduction. Excessive ingestion of iron-containing vitamins can cause toxicity; it is estimated there are 26 500 cases of iron overdose per year in the US *(4)*. Inappropriate handling of these commonly available products can cause overuse and, rarely, toxicity. The patient presents with nonspecific symptoms of gastrointestinal distress and bleeding and cardiac rhythm disturbance. The history and clinical examination in the ED are the keys to identifying these toxic agents. Serum or plasma iron analysis, readily available from most clinical laboratories, is useful to identify an iron overdose.

Recommendation. The clinical laboratory should be prepared to provide serum or plasma iron results on a stat basis to aid in the diagnosis of iron overdose. Because of analytical limitations, heterogeneous assays for the total iron-binding capacity (TIBC) cannot be used to determine the absence of free iron and toxicity. Serum or plasma transferrin is a more reliable marker for estimating free and potentially toxic iron. If this assay is not available on a stat basis, the homogeneous unsaturated iron-binding capacity (UIBC) assay is more useful than TIBC assays that require a pretreatment step. *Degree of consensus: A*

Discussion. Serum or plasma iron analysis, readily available in most clinical laboratories, is useful to identify iron overdose; serum/plasma iron >3500 μg/L (350 μg/dL) indicates significant exposure *(89)*. If the serum/plasma iron concentration exceeds the TIBC, it has been presumed that there is free and potentially toxic iron. However, TIBC tests that require separation of transferrin-bound iron from the added adsorbent can overestimate TIBC, producing a falsely low free-iron value *(90)* and an incorrect assumption that there is no risk for iron toxicity *(91)*. Measurement of transferrin is the preferred test (1 μmol of transferrin binds 2 μmol of iron). If this test is not available, direct UIBC assays are less susceptible to falsely high results attributable to iron overdose *(92)*. Some patients with an iron overdose are treated with deferoxamine. It should be noted that this chelator will interfere with some dye-binding colorimetric iron methods, producing falsely low iron results *(93)*. The Committee recommends that blood specimens be taken for iron determination before deferoxamine administration. Alternatively, an assay based on atomic absorption spectrometry can be used without interference from this chelator.

f. arsenic and mercury

Introduction. Significant arsenic exposure results from occupational sources, malicious poisoning, or water contamination by arsenic-bearing ore. At one time, arsenic was widely used as a rodenticide, pesticide, and herbicide and for treating wood for outdoor use. Industrial arsenic exposure results from dusts and fumes generated in connection with the smelting of copper, lead, and other iron ores. Acute arsenic poisoning can be fatal, usually as a result of heart failure. Arsenic exposure can also produce renal, neurologic, and hematologic disorders.

Mercury is found in four principal forms: elemental, mercury salts, alkyl mercury, and aryl mercury compounds. Mercury exposure can lead to neurologic impairment, renal tubular acidosis, and gastrointestinal symptoms. Mercury is found in thermometers, barometers, dental amalgam, and seafood. Arsenic or mercury rarely contribute to significant acute toxicities, and testing is not useful to support ED practice.

Recommendation. A 12- or 24-h timed urine collection in a metal-free container (use opaque plastics with no metal caps) is the best sample for arsenic and mercury analysis and falls outside the realm of ED practices. Results of urine testing should be available within 48 h of specimen collection. *Degree of consensus: A*

Discussion. Timed urine is the specimen of choice to identify the exposure and body burden of arsenic and mercury and the need for chelation therapy *(94)*. These tests are not generally available from the clinical laboratory; they are provided by reference laboratories. At this time, obtaining a general trace metals screen in asymptomatic individuals or those without a history of recent exposure is inappropriate. Therapeutic protocols to manage patients with inconsequential but detectable heavy metal concentrations are also not recommended without adequate evidence of either safety or efficacy. Testing of workers who have occupational exposures to heavy metals, however, may be appropriate *(95)*. There is no current role for blood testing for these metals except in cases of very recent, heavy exposure.

g. broad-spectrum screening for trace elements and environmental pollutants

Introduction. These panels of tests were defined by the Committee as uncommonly performed laboratory analyses for trace elements, environmental contaminants, or endogenous enzymes obtained from samples of blood, urine, hair, or other body tissues (e.g., boron or selenium, environmental contaminants such as phthalates and ali-

phatic hydrocarbons, and analytes such as mercapturic acid). These tests or matrices generally lack a published report of validated reference intervals or suffer from major procedural difficulties. At this time, many of these are best used as research tools, such as the current population evaluations by the National Center for Environmental Health of the CDC *(96)*. Application of these test results to individual patients is fraught with problems. In addition to problems with patient preparation and specimen collection, analysis, reliability, and reporting issues, there are practitioners and laboratories that provide diagnoses of heavy metal poisoning or trace element excesses or deficiencies to healthy individuals and then prescribe expensive tailored treatments from their offices.

Recommendation. In the absence of probable cause, such as occupational and/or accidental environmental exposure, broad-spectrum screening for trace elements or other analytes is inappropriate and would rarely be indicated in the ED or any general office practice. These tests have not been sufficiently validated in a general patient population, nor have the implications of clinical decisions based on one-time measurements been discussed sufficiently to warrant any use other than research and biomonitoring for occupational exposure. *Degree of consensus: B*

Discussion. The Committee's concern is that laboratory standards are not available for these studies outside the research setting or possibly monitoring of known (usually occupational) exposures. Some of the data that are lacking include limits of detection and quantification, true population range, applicability of one medium to another [e.g., hair, urine, saliva, serum, plasma, red blood cell (RBC) mass], method of collection, stability during transport, and sensitivity or specificity for disease *(97)*. Of major concern to the Committee are the financial connections some treating practitioners have with the testing laboratories.

The status of this recommendation will change as laboratories provide more information regarding standardization *(98)*. In addition, the NHANES studies should provide better population estimates for many of these measurements *(96)*. The Agency for Toxic Substances and Disease Registry has indicated that there is sufficient evidence for the value of hair analysis for individuals potentially exposed to methylmercury, particularly children *(99)*. Even so, this analysis should be based on an appropriate clinical evaluation *(100)*. Until these concerns can be resolved with research and clinical studies, biomonitoring other than for occupational exposure is not recommended.

H. PESTICIDES

Introduction. Carbamates and organophosphates such as diazinon, chlorpyrifos, parathion, and malathion are popular pesticides used in the agricultural industry. Carbamates and organophosphates inhibit cholinesterase at cholinergic synapses, thereby preventing degradation of the neurotransmitter acetylcholine. Excess acetylcholine at neuroeffector (muscarinic) myoneural junctions and autonomic ganglia (nicotinic) produces such symptoms as bradycardia, bronchorrhea, lacrimation, salivation, emesis, diarrhea, diaphoresis, fasciculation, and muscle paralysis. Atropine is used to compete with acetylcholine for muscarinic receptors, thereby protecting the end organs from excess acetylcholine, whereas pralidoxime is effective in treating both muscarinic and nicotinic symptoms. Patients exposed to substances that produce cholinergic response can be screened for the presence of low pseudocholinesterase activity *(101)*. However, this test is not specific for cholinergics, as depressed activity can be attributable to genetic variability and chronic liver diseases *(102)*. The dibucaine inhibition test can identify such variants. RBC cholinesterase activity is the definitive test to document exposure to cholinergic agents.

Recommendation. Clinical laboratories should provide access to stat pseudocholinesterase testing to screen for exposure to cholinergic agents and not for monitoring of therapy. *Degree of consensus: B*

Discussion. The Committee recognizes that most laboratories will not have the RBC cholinesterase test because it is a very difficult test to perform and because it is needed infrequently. In a survey of participants attending the AACC meeting, only ~20% of attendees stated that they had the ability to perform the RBC cholinesterase test. Thus, reference laboratories are the usual providers of RBC cholinesterase tests, and results should be made available within 24–48 h. Reagents for serum/plasma pseudocholinesterase tests are more available. Roughly one-half of the participants of the AACC meeting indicated capability of this testing. Results should be made available with a target TAT of 4 h. However, because of low testing volumes, many small laboratories cannot justify the expense. Although it is recognized that pseudocholinesterase activity is influenced by many factors, such as genetic polymorphisms, nutritional status, medications, and liver function, the test is useful to address whether the patient has been exposed to a cholinergic agent *(103)*. Furthermore, given recent increased concern regarding chemical and biological terrorism, such screening tests may become part of a clinical laboratory's support to state agencies, given that nerve agents are potent organophosphates *(104)*.

I. INHALANTS

Introduction. Inhalants are popular substances that are abused by children and adolescents. Aromatic hydrocarbons such as toluene are found in solvents, paint thinners, and plastic cements. These volatile compounds produce euphoria and hallucinations similar to other stimulants. There are several CNS manifestations of inhalant abuse,

including dizziness, blurred vision, violent behavior, tremors, and convulsions *(105)*. Long-term abuse can lead to learning deficits *(106)*. Other organic solvents, such as benzene, carbon tetrachloride, chloroform, xylene, acetonitrile, and formaldehyde, can also produce toxicity and are hazards within particular occupations.

Recommendation. Because of a lack of stat availability, there are no clinical laboratory tests that are currently appropriate for monitoring acute inhalant abuse or solvent exposure. *Degree of consensus: A*

Discussion. ED personnel should be cognizant of signs of inhalant abuse. Clues to inhalant abuse include chronic sore throat, cough, and runny nose; unexplained listlessness, moodiness, weight loss, bloodshot eyes, and/or blurred vision; and chemical odors on the breath, hair, bed linen, and clothes. Oral and nasal ulcerations or a rash around the mouth ("glue sniffer's rash") may be observed. Occasionally the products themselves may be discovered in the room of the abuser or as residua about the nose, mouth, and hands *(107)*. Toluene and benzene metabolize principally to hippuric acid and phenol *(108)*, respectively. The presence of increased concentrations of hippuric acid is not specific to inhalant abuse because certain foods and beverages also contain benzoate *(109)*. Urinary phenol concentrations can increase with the consumption of some over-the-counter drugs, such as Pepto-Bismol and Chloraseptic *(110)*. More specific urinary metabolites have been studied for toluene, such as *o*-cresol *(111)*, *S-p*-toluylmercapturic acid *(112)*, and trace concentrations of toluene itself *(113)*, and for benzene, such as *trans*-muconic acid and *S*-phenylmercapturic acid *(114)*. Assays for these metabolites are not in routine use at clinical laboratories. Thus samples must be sent to specialty laboratories where the TAT makes them impractical for critical care management. In addition, there are currently no guidelines for the interpretation of results.

J. METHEMOGLOBINEMIA

Introduction. There are several drugs and toxic agents that can oxidize hemoglobin to methemoglobin, such as nitrates, chlorates, quinones, phenacetin, sulfonamides, aniline dyes, and local anesthetics such as procaine, benzocaine, and lidocaine *(115)*. Methemoglobin is unable to bind oxygen because the heme group is oxidized to the ferric state. Monitoring of oxygen saturation by pulse oximetry (where two spectrophotometric wavelengths are used to measure the fraction of oxyhemoglobin from oxy- and deoxyhemoglobin) is insensitive to methemoglobin. Co-oximetry typically uses four wavelengths to discriminate oxyhemoglobin from oxy-, deoxy-, carboxy-, and methemoglobin.

Recommendation. For patients suspected of having methemoglobinemia, measurement of the fraction of oxyhemoglobin (oxygen saturation) should be performed with a co-oximeter and not a pulse oximeter, as the latter overestimates the actual O_2 saturation. If a request for oxygen saturation is received, all results of a four-part co-oximetry panel should be reported even if the specific requests for carboxyhemoglobin and methemoglobin are not received. Laboratories should not charge separately for the inclusion of these additional results. *Degree of consensus: A*

Discussion. Numerous studies have shown that pulse oximetry is not an accurate measure of methemoglobinemia *(116, 117)*. At low methemoglobin concentrations, oxygen saturation as measured by pulse oximetry is slightly higher that the actual value (e.g., 10% methemoglobin produces 95% O_2 saturation instead of 90%). When the methemoglobin concentration exceeds 35%, O_2 saturation by pulse oximetry will be significantly overestimated because O_2 saturation reaches a plateau of 85% and becomes independent of methemoglobin concentration. In this situation, the patient will generally appear cyanotic with a falsely increased pulse oximeter reading, unless the methemoglobinemia is also accompanied by hemolysis. Because in co-oximetry extra wavelengths are monitored, O_2 saturation is measured accurately in the presence of various methemoglobin concentrations. In the presence of methylene blue, which is used to treat patients with methemoglobin, falsely low readings can occur by both pulse and co-oximetry *(118)* because methylene blue has a high absorbance at the methemoglobin absorbance maximum.

K. REGIONAL TOXICOLOGY CENTERS

Introduction. As evidenced by the discussion in this document, most laboratories will not be able to meet all of the needs of an ED in their workup of all intoxicated and overdosed patients. Some analytes require sophisticated methodologies that are expensive to acquire or difficult to maintain and operate on a 24-h basis. Many instruments require very highly trained laboratory personnel. The low volume of testing does not justify the expense of providing the service. The lack of a commercial immunoassay for particular analytes (e.g., fentanyl, ketamine, and GHB) also limits the availability of testing. Even the largest hospital laboratories will have difficulty in providing the testing needed for all clinical circumstances.

Recommendation. A cooperative effort should be made to establish regional toxicology centers where specialized methods can be made available to service the toxicologic needs of a larger community of medical centers. *Degree of consensus: A*

Discussion. The success of a regional center will depend on good cooperation among facilities and the proximity of the center to the clinical sites. To be useful in real time, it is important that samples be delivered, tested, and reported within a few hours after collection. Many reference laboratories have full-service toxicology capabilities and

can serve as regional centers for nearby hospitals. For areas where there are no reference laboratories in close proximity, a regional hospital toxicology laboratory would be desirable. To be economically viable, a commitment would be needed that all regional toxicology testing is sent to this central facility and that a reasonable reporting TAT (e.g., 4 h) is met. It would be the responsibility of laboratory and hospital administrators to establish the facility and maintain its viability. Where appropriate, regional poison control centers may be helpful in publicizing and referring facilities to the regional laboratories. These public health information and poison treatment resources can also assist in the development of protocols and cooperation among institutions. A nationwide toll-free telephone number (1-800-222-1222) and internet site (www.aappc.org) have been established to facilitate contact with the nearest regional poison control center.

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