Supporting the Emergency Department

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Introduction

The goal of emergency toxicology is to provide *clinically useful* toxicology test results to support the needs of the poisoned patients in the emergency department (ED). The clinical usefulness of the results refers not only to the clinical utility of testing, but also to the timeliness of reporting toxicology results.

Due to the complexity of the diagnosis and treatment of poisoning, toxicology results, if available at the appropriate time, can influence the diagnosis and subsequent treatment of the poisoned patient. Emergency toxicology tests can validate drug history or identify drugs and toxins that are not previously suspected. Rapid laboratory identification or confirmation of the toxic agents is invaluable for those cases in which specific treatment is available and its prompt institution is critical: for example, *N*-acetylcysteine therapy for acetaminophen overdose, and ethanol or fomepizole infusion for methanol and ethylene glycol poisoning. Serum drug levels, in some instances, can be helpful in gauging the severity of intoxication and the need to initiate specific interventions, and ensuing determinations can be useful in monitoring and evaluating the effectiveness of the treatment procedure.

It is unrealistic to expect any clinical laboratory to provide a full spectrum of toxicological analyses in real time, mostly because of cost constraints and staffing problems. The laboratory and the ED should jointly decide on a toxicology service that is feasible within the financial and technical capability of the laboratory, and one that can still meet the basic needs of the treating physicians. The essential features that need to be considered include the following: (1) which drug assays should be available, (2) whether the assays should be qualitative or quantitative, (3) which specimen types (serum, urine, etc) to use, (4) when the specimen should be obtained, and (5) what turnaround time (TAT) is acceptable.

There are published guidelines that address these issues and make recommendations regarding which serum or plasma and urine tests have the greatest impact on patient management and can be realistically delivered. The National Academy of Clinical Biochemistry (NACB) and others recommended that the hospital clinical laboratory provide two tiers of toxicology testing.[1] Tier 1 tests include select serum or plasma quantitative tests and urine qualitative tests. These tests should be available at all times, on a stat basis, in any clinical laboratory that supports an active ED, regardless of size or setting (rural or urban) of the institution. Tier 2 tests detect drugs or toxins not identified by Tier 1 tests, are more complicated and time consuming to perform, and may be referred to a reference laboratory.

Tier 1 Tests

The Tier 1 tests should be considered as the toxicology service essential to the support of an ED. Any clinical laboratory, including those that do not have advanced instrumentation, can provide these tests. Selection of the serum quantitative and urine qualitative tests should be based on the prevalence of these drugs and toxins in the population served by the ED, the clinical usefulness of their early identification or quantitation, and the ability of the laboratory to perform the analyses with an acceptable TAT. The ED and the laboratory should jointly determine the list of Tier 1 tests. For example, some EDs may choose not to include cannabinoids (tetrahydrocannabinol [THC]) as part of their routine urine drug panel if it provides difficulties for follow up, does not contribute significantly to the clinical picture, and could therefore provide a cost savings to the laboratory. However, other hospitals such as a dedi-

cated children's hospital may want this analyte included on an initial screening panel because many consider it a "gateway" drug and most pediatricians are willing to follow up with parents. In any regard, THC should be available on the requisition list as a separate test for any practitioners who require it. Another consideration in determining a laboratory-specific test menu is the geographic utilization of certain drugs. For example, phencyclidine (PCP) is not widely used in the northeastern US and therefore might not be included on the test menu if both the ED and the toxicology laboratory agree (author's experience). What is most important is that there be a discussion between the laboratory and the ED to identify which tests are needed. Other considerations include the changing landscape of available drugs in the United States. In November 2010, the Food and Drug Administration notified health care professionals that propoxyphene was to be withdrawn from the market. This decision was based on evidence that the drug, even at therapeutic doses, can produce significant cardiac toxicity. Initial NACB guidelines included propoxyphene, but given that the number of patients receiving this drug will drastically be reduced, with time, the need for testing for propoxyphene will have to be reassessed.

It is also important for the ED and the toxicology laboratory to have the same definition of an acceptable TAT and to agree on a target TAT within which the laboratory can receive specimens and reasonably complete the analysis and report the results that are still clinically relevant to the acute care of an ED patient. Many consider 1 hour or less as the recommended time for Tier 1 tests, but this may be difficult to meet for some laboratories.[1] TAT is usually measured from the time the specimen reaches the laboratory until the time the result is reported. Specimens that are collected in the ED and then "sit" for a period of time are a potential source of frustration for both ED and laboratory staff. Every attempt should be made to send specimens as quickly as possible to the laboratory after they are collected. In an effort to reduce TAT, some laboratories may choose to use point-of-care testing (POCT) in order to accommodate a TAT of 1 hour or less. One study demonstrated a reduction in TAT from 108 to 33 minutes when testing was switched from the core laboratory to POCT[2]; however, this testing was at least twice as expensive as that in the core laboratory (unit-cost basis) and increased the use of drugs-of-abuse testing, thereby increasing the cost of testing overall. Nevertheless, the increased cost of the POCT could be offset by the reduction in the length of stay in the ED. It is incumbent upon each laboratory to determine if the benefits of saving a small amount of time will actually translate into an overall savings for the hospital. Additional considerations when using POCT in the ED revolve around which department performs, and has responsibility for, these laboratory tests. Options include having the ED laboratory as a satellite of the core laboratory (ie, it is staffed and operated by the laboratory personnel) or having the laboratory operated by ED staff with the core clinical laboratory providing oversight. It is important in this regard to make sure the ED staff have demonstrated training and annual competency, and follow all the regulatory components necessary for laboratory accreditation.

With regard to analysis of other matrices, first gastric aspirate, vomitus, or stomach washings are useful specimens if they are obtained soon after ingestion and if pill fragments are noted; however, the analysis of gastric contents offers no advantage over urine, and, furthermore, drugs that are rapidly absorbed or that are not taken orally will not be detected. Oral fluid has been used successfully for alcohol testing. Widespread adaptation of oral fluid for drugs-of-abuse testing in the United States has been limited by the novelty of the analytical technology and the lack of extensive user experience. These factors will change with time, and the future of oral fluid as a specimen for clinical toxicology is promising.

Quantitative Serum Tests

Quantitative measurement of serum drug concentration is meaningful if drug concentration is correlated to toxicity or if knowledge of a specific drug concentration level influences patient management. Serum tests suggested by the NACB guidelines that meet the above criteria are *acetaminophen, salicylate, carbamazepine, valproate, phenobarbital, theophylline, digoxin, lithium, iron, transferrin (or total iron-binding capacity [TIBC]),* and *ethanol,* and co-oximetry for *carboxyhemoglobin* and *methemoglobin* (Table 2-1). Implementation of these quantitative serum tests in any laboratory supporting emergency medical care is feasible because these tests are usually available either as therapeutic drug monitoring assays (eg, digoxin, lithium) or clinical chemistry tests (eg, iron) in most, if not all, clinical chemistry laboratories.

Given the effectiveness of fomepizole as an antidote for methanol and ethylene glycol (EG) poisoning and the importance of early identification of methanol and EG, the quantitative assays for methanol and EG should be Tier 1 tests. Unfortunately, on-site availability of these tests is severely limited by the technical difficulties of the chromatographic methodologies, making them unavailable as Tier 1 tests in most hospital-based laboratories. Therefore, each hospital laboratory should

Table 2-1. Stat Quantitative Serum Toxicology Assays Required to Support an Emergency Department
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 unsaturated iron-binding capacity [UIBC] assay if transferrin is not available)
Ethyl alcohol
Methyl alcohol
Ethylene glycol

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have a reference laboratory or regional center where these tests can be referred if needed. In addition, there are enzymatic assays currently available for EG,[3] and these may provide a useful screening to rule out the presence of EG. Given that the test may be positive in the presence of increased lactic acid or lactate dehydrogenase activity,[4] positive screening tests should be confirmed by an alternate, more specific method, such as gas chromatography. An additional test that may provide useful information in overdoses of volatile substances (including EG) is the osmolal gap, which requires both the measured osmolality and calculated serum osmolarity[5,6] (Figure 2-1).

Osmolal Gap = Measured Osmolality – Calculated Osmolarity

The reference interval = 0 +/– 5-10

Calculated osmolarity = 2[sodium] + [glucose]/18 + [BUN]/2.8 = ~290 mOsm/L

Serum sodium is in mEq/L, and glucose and BUN (blood urea nitrogen) are measured in mg/L

Both measured osmolality and calculated serum osmolarity should be obtained from the **same** serum sample

Figure 2-1. How to calculate the osmolal gap.
See chapter 23, *Non-Ethanol Volatiles and Ethylene Glycol,* for more details.

Table 2-2. Stat Qualitative Urine Toxicology Assays Required to Support the Emergency Department
Cocaine
Opiates
Barbiturates
Amphetamines
Propoxyphene
Phencyclidine (PCP)
Tricyclic antidepressants

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Urine Qualitative Tests

The urine immunoassays for drugs of abuse are available as reagent kits for automated chemistry instruments or as POCT devices. These assays are used extensively because they can be performed at any time of the day and require low to moderate technical expertise.

There is a lack of consensus among clinical toxicology experts on the usefulness of a qualitative urine drug screen, and in particular, one that is composed of immunoassays for the common drugs of abuse (Table 2-2). Relevant issues include the poor specificity (inaccuracy) of the immunoassays,[7,8] the lack of correlation between the presence of drug or metabolite in urine and the toxic effects or clinical impairment, and the extended window of detection of drugs or metabolites after the most recent use. Therefore, there is the perception that a urine drug screen has little impact on the acute care of a poisoned patient and that the screen serves more of a confirmatory or documentation purpose. Nevertheless, the use of a urine drug screen performed stat in emergency toxicology is widespread in the United States, and laboratory professionals are advised to consult the chapters on specific drug groups for the pharmacokinetic and toxicokinetic properties of these drugs, and chapter 10, *Analytical Methodologies for the Toxicology Laboratory,* for detailed discussions on the limitations of immunoassay-based drug screens.

Tier 2 Tests

For intoxicated patients whose clinical signs cannot be explained by the Tier 1 agents, additional tests (Tier 2 tests) can be useful in identifying other agents that have clinical significance, for example, a more broad-spectrum drug screen or a trace metal analysis. These tests require complex analytical techniques (chroma-

Release of Laboratory Specimens and Release of Laboratory Specimens Form

Hospital Name

Hospital Name **Department of Pathology and Laboratory Medicine Policy**	**Subject:** Release of Laboratory Specimens	**File Under:** *Department of Pathology Laboratory Administration Policy Manual*
Issuing Area: Laboratory Administration		**Latest Revision Date:**
Original Procedure Date:	**Page 1 of 1**	**Approved By:** Chief of Pathology Director of Laboratory Services

I. Purpose
The purpose of this policy is to define the process of releasing laboratory specimens to outside agencies.

II. Eligibility
All staff of the Department of Pathology and Laboratory Medicine.

III. Forms
Release of Laboratory Specimen Form

IV. Policy
The laboratory is frequently asked to release patient-related specimens to other agencies for the purposes of further or confirmatory testing. It is the policy of the Hospital Name Department of Pathology and Laboratory Medicine that specimens can be released directly to an authorized agent of the Medical Examiner's Office/Coroner or an authorized agent of the XX Organ Bank. This is only after these representatives have been properly identified and after the completion of the *Release of Laboratory Specimens Form.*

Other individuals seeking to obtain specimens for legal purposes must have either a search warrant or a subpoena from the State/Commonwealth of XX specifying these requests. If issued either a search warrant or a subpoena, these should be faxed directly to the Hospital Name Risk Management Department for review before release of the specimens. Once approved by the Risk Management Department, the *Release of Laboratory Specimens Form* should be completed.

Author: **Date:**

Figure 2-2. Example of a policy for release of laboratory specimens.

tography, atomic absorption spectrophotometry, mass spectrometry, etc), sophisticated expertise, and highly trained staff. Many of these tests are done infrequently, even in the largest hospitals, making it difficult to maintain competency and justify the costs of doing these tests. Tier 2 tests can be done on site, in a nearby laboratory, at a regional center, or in a reference laboratory. A cooperative effort undertaken to develop a regional toxicology center can provide a full spectrum of advanced toxicology service to support regional hospitals. The regional laboratory system has the advantages of avoiding duplication of laboratory facilities and of pooling regional workload to sustain proficiency in difficult, low-volume tests.

Unique Challenges Associated with Testing in the ED

Many victims of trauma—including those resulting from gun shots, stabbings, or motor vehicle accidents—or persons suspected of driving under the influence (DUI) will have some form of drug testing while in the ED. These cases, in addition to patients who may succumb to drug overdose or accidental poisoning, will necessitate the involvement of other outside agencies, including law enforcement or the medical examiner/coroner. Although drug testing in the ED is obtained to support and validate clinical findings, sometimes these results will be used in court in either criminal or

Hospital Name

Department of Pathology and Laboratory Medicine
Release of Laboratory Specimens Form

Patient's Name	
Patient's Medical Record Number	
Date of Specimen	
Agency Requesting Sample	
Agency Representative (printed name)	
Agency Representative (signature)	
Date of Request	

Below for Laboratory Use Only

Specimen Type(s)	
Accession Number(s) Released	
Technologist's Name	
Date	
Laboratory	
Supervisor's Initials and Date	

Figure 2-3. Example of a form for release of laboratory specimens.

civil cases or will help to determine the cause of death; the reader is referred to chapter 6, *The Hospital Autopsy and Toxicology Testing*. In these circumstances, it will be necessary for the laboratory to provide documentation of testing, results obtained, methodology used, and/or quality control results, if requested, by law. In addition, the laboratory may be asked to provide any residual serum or urine specimens to the medical examiner/coroner, state police, or some other governmental agency. In consideration of the possible need for further testing in these types of cases, the ED and the laboratory may want to discuss an arrangement whereby an additional "gray top" or sodium fluoride/potassium oxalate tube is collected from the patient during the ED visit. Furthermore, clinical laboratories should keep a record of what specimens were released as well as to whom they were released. Each laboratory should check for compliance with both the Health Insurance Portability and Accountability Act (HIPAA) and the hospital legal or risk division as to how this information should be documented. It is important to note, however, that medical examiners/coroners have a specific exclusion within the HIPAA law, in that any and all information requested in a death investigation must be released to these offices as requested.[9] An example of a policy for the release of specimens and the accompanying form can be found in Figures 2-2 and 2-3.

The clinical laboratory should be aware that a Supreme Court decision, *Melendez-Diaz v Massachusetts*,[10] now makes it more likely that laboratorians,

Table 2-3. Common Toxidromes, Toxic Symptoms, Toxidrome Agents, and Antidotes

Toxidrome	Signs and Symptoms	Common Toxidrome Agents	Antidotes
Anticholinergic	Red as a beet (erythema) Dry skin Delirium Mydriasis Hyperthermia Bowel and bladder (urgency and retention) Tachycardia	Jimson weed Antihistamines Phenothiazines Tricyclic antidepressants Over-the-counter sleep aids (antihistamines)	
Cholinergic, muscarinic	D- Diarrhea U- Urination M- Miosis B- Bradycardia/bronchorrhea E- Emesis L- Lacrimation S- Salivation	Organophosphates Some mushrooms *(Amanita muscaria)*	
Cholinergic, nicotinic	Nausea Vomiting Tachycardia Hypertension Muscle fasciculations Weakness or paralysis	Nicotine insecticides Tobacco Black widow spider venom Carbamates	
Opioid (narcotic)	Central nervous system depression Miosis Hypotension Hypoventilation	Codeine Morphine Heroin Oxycodone Hydrocodone Meperidine Fentanyl	Naloxone

technicians, and technologists will be called to testify in court if they have been involved in the analysis or acquisition of specimens related to criminal (or civil litigation) cases (ie, homicides, DUI cases). Therefore, it is recommended that laboratory personnel gain knowledge about testimony procedure if required to go to court. In these cases, the laboratory personnel can testify to obtaining a tube of blood or a container of urine labeled with the patient's name (eg, Jane Doe, MR # 123456). Unless the laboratory technologist personally collected the specimen from Jane Doe, he or she cannot testify in court that the specimen is actually from "Jane Doe," but rather that the tube is labeled with Jane Doe's name. Although most clinical laboratories do not require chain of custody, all laboratories engaged in forensic toxicology testing should practice strict chain-of-custody procedures, which would eliminate this awkward predicament.

Toxidromes

Historically, physicians and laboratory personnel were taught toxidromes, that is, signs and symptoms associated with a specific poison or drug. When considering a specific toxidrome, not only are the heart rate, respiratory rate, temperature, skin color, and pupil size of significance, but it is also important to take into consideration any odors associated with the patient (either on clothes, breath, or body). Certain drugs or their metabolites may produce a specific odor that may point to the culprit drug.

However, toxidromes have become more difficult to identify in the acutely intoxicated patient, and this is primarily due to *polypharmacy*. Patients may ingest multiple drugs from different classes and present with seemingly mixed toxidromes—for example, drugs from the sedative-hypnotics class (benzodiazepines) or opioid toxidrome mixed with those of the sympathetic tox-

Table 2-4. Commonly Encountered Toxic Agents

Toxic Agent	Signs and Symptoms	Supportive Laboratory Tests	Antidotes
Acetaminophen (Tylenol compounds)	**Phase 1:** Vomiting, nausea, gastrointestinal irritability, diaphoresis, and pallor. May last 12-24 hours. **Phase 2:** Latent period. Slight improvement, but right upper quadrant pain, rise in liver function tests (LFTs). **Phase 3:** Hepatic necrosis; increased LFTs, prothrombin time (PT), encephalopathy, death.	Serum acetaminophen concentration 4 or more hours after a single ingestion Aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, PT (international normalized ratio [INR]), lactate, serum creatinine, electrolytes, phosphate, human chorionic gonadotropin (hCG) where appropriate as acetaminophen crosses the placenta Arterial blood gas	*N*-acetylcysteine (NAC) (FDA approved for PO or IV administration) as appropriate
Salicylates (aspirin compounds)	**Acute overdose:** nausea, vomiting, abdominal pain, tinnitus at concentrations >20 mg/dl, coma, seizures	Serum salicylate concentration obtained 2 hours after ingestion Electrolytes, glucose, blood urea nitrogen (BUN), creatinine, baseline LFTs	
Iron	Stage 1 (gastrointestinal) Stage 2 (latent) Stage 3 (metabolic/cardiovascular) Stage 4 (hepatic) Stage 5 (delayed)	Serum iron concentration 4 hours after ingestion Glucose, CBC, lactate, arterial blood gas, coagulation studies (PT), LFTs, electrolytes, hCG where appropriate	Deferoxamine
Cyanide	**Moderate exposure:** palpitations, dizziness, gastrointestinal symptoms, headache, hyperventilation **High exposure:** syncope, coma, seizures, cardiovascular collapse	Cyanide concentration	Cyanide antidote kit (amyl nitrite pearls, sodium nitrite, and sodium thiosulfate pearls)
Methanol (windshield washer fluid)	Ethanol-like intoxication, gastritis Visual disturbances, seizures, acute renal failure	Methanol concentration Measure osmolar gap Electrolytes (look for severe anion gap metabolic acidosis)	Ethanol Fomepizole (methylpyrazole or 4-methylpyrazole [4-MP])
Ethylene glycol (antifreeze)	Ethanol-like intoxication, gastritis Seizures, dysrhythmias	Ethylene glycol concentration Osmolar gap Electrolytes (anion gap metabolic acidosis), calcium	Ethanol Fomepizole (methylpyrazole or 4-MP)

idrome (cocaine or amphetamines). *The DAWN Report* from 2009 revealed that there were approximately 4.6 million drug-related ED visits, of which about one-half were attributed to adverse reactions to pharmaceuticals and one-half to drug misuse or abuse[11] (for more information the reader is referred to chapter 8, *Adverse Drug Events, Poisonings, and Abuse*). Not surprisingly, ED visits involving misuse or abuse of pharmaceuticals from 2004 until 2009 nearly doubled. In addition, when considering the application of toxidromes in the unconscious patient, the background prevalence of a specific agent should be considered. Specific geographic locations (even within a city) may mean that the availability of certain drugs would more likely produce the clinical presentation of the toxidrome than would another drug.[12]

Sympathetic, parasympathetic (cholinergic; muscarinic and nicotinic), anticholinergic, and opioid (narcotic) toxidromes are the most common. Thumbnail outlines of the classic toxidromes are found in Table 2-3; additional toxic agents commonly encountered in the ED are found in Table 2-4.[13-18] For detailed infor-

mation about various drug classes or toxic agents, the reader is referred to the individual chapters within this book.

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