WHAT YOU NEED TO KNOW FOR AN INITIAL OVERDOSE CONSULT

REFER TO DETAILED HANDOUT FOR A MORE COMPREHENSIVE UNDERSTANDING

Acetaminophen

- Laboratory Medicine Resident informed for any value > 50 µg/ml

- Any single dose or accumulated daily dosage of 7.5 grams in adults (or 150 mg/kg in children) is considered potentially toxic and further evaluation for emergency treatment is recommended. This screening cutoff is considered very conservative and, in most cases, adult doses exceeding 12 g/day are required for significant hepato-toxicity

- In an overdose (especially with extended release formulations) up to four hours may be required for peak levels

- The initial symptoms of acetaminophen overdose are minimal. Only mild anorexia, nausea, pallor, vomiting, diaphoresis and malaise may be present in the first 24 hours, or the patient may be entirely asymptomatic. Hepatic damage begins to manifest after 24-72 hours. Right upper quadrant pain may be present and the appropriate blood chemistries become abnormal. Hepatic necrosis and fulminant failure occur after 72 hours. Multi-organ failure is a consequence of fulminant hepatic failure (cerebral edema, renal failure, ARDS, etc.); hence, it is has been difficult to assess whether NAPQI contributes to non-hepatic organ failure

- Once a suspicion of toxic ingestion has been established, laboratory testing for acetaminophen concentration and AST is recommended

- The recommended U.S. threshold for risk of hepatotoxicity begins at an acetaminophen concentration of 150 µg/ml at 4 hours post-ingestion, declines to 75 µg/ml at 8 hours, 37.5 µg/ml at 12 hours, etc. The cutoffs are highly sensitive such that any patient maintaining acetaminophen levels below the line is considered to have virtually no risk for subsequent liver damage

- A second acetaminophen level, drawn approximately 4 hours after the first level, is often obtained. The second level assures complete absorption and can exceed the threshold for therapy even when the first level appeared below the line. A second level also allows estimation of an elimination half-life

- NAC therapy initiated within 8 hours after an acute acetaminophen ingestion is nearly completely protective. Liver damage is only expected when there is delay in the administration of therapy. Even after signs of hepatotoxicity, NAC therapy appears effective at limiting the extent of liver damage and is recommended.

- Serum or plasma acetaminophen levels are provided 24 hours a day and performed by EMIT on the Roche Modular analyzers. Results are reportable from 1-300 µg/ml and are linear up to 200 µg/ml. There are no significant cross-reactivities nor negative interferences, except for severe hypertriglyceridemia, which is routinely removed by ultracentrifugation before analysis

Salicylate

- Laboratory Medicine Resident informed for any value > 30 mg/dl

- The earliest signs and symptoms of salicylate toxicity include nausea, vomiting, diaphoresis and tinnitus. Other early CNS effects may include vertigo, hyperventilation, hyperactivity, agitation, delirium, hallucinations, convulsion, lethargy, stupor and, rarely, coma (suspect either massive ingestion of mixed overdose). Confusion of the symptoms of salicylate poisoning with other illnesses frequently occurs.

- Salicylate poisoning results in a mixed respiratory alkalosis and wide anion gap metabolic acidosis, although variations in presentations occur (Refer to handout for detail)

- Presentation may include hypoglycemia, hepatitis (especially in children), pulmonary edema, platelet dysfunction, hyperprothrombinemia and anemia

- Nausea, vomiting, hemorrhagic gastritis, decreased gastric motility and pylorospasm occur with both acute overdoses and chronic salicylate use. These effects are more pronounced in the elderly

- Eventual hearing loss preceded by tinnitus occurs with serum salicylate concentrations over 20-40 mg/dl. This is considered one of the most consistent and specific early symptom of salicylate poisoning

- Although serum or plasma salicylate concentrations are useful for identifying patients who may have overdosed on salicylates, the severity of toxicity correlates poorly with measured levels

- A decrease in pH results in increased neutral salicylate with increased partitioning into tissue where toxicity may increase. Hence, observation of a decrease in the serum salicylate concentration concomitant with a decrease in blood pH may indicate a worsening situation as drug is shifted to tissue, increasing toxicity and subsequently further reducing blood pH

- Alkanization of both serum and urine by administration of parenteral sodium bicarbonate is critical for the treatment of a salicylate overdose. Alkanization of the urine is more dramatic than in serum as the pH of urine may vary from 4.5 to 8.0 resulting in 10-20 fold increase in the renal clearance of salicylate. For severe poisonings, extracorporeal removal of salicylates should be considered either by hemodialysis (preferred) or hemoperfusion

- Serum or plasma salicylate concentrations are measured quantitatively on the Roche Modular Analyzer utilizing the enzyme salicylate hydroxylase which catalyzes the conversion of salicylate to catechol using NADH as an electron donor (oxygen is converted to water during the reaction). The resulting decrease in absorbance at 340 nm, due to conversion of NADH to NAD+, is directly proportional to the concentration of salicylate in the sample. The assay is available 24 hours a day. There are no significant cross reactivities nor interferents (except severe hypertriglyceridemia, which is removed by ultracentrifugation before analysis)

Tricyclic Antidepressants

- All the first generation antidepressants are highly toxic and have been one of the leading causes of mortality from a prescription drug overdose

- Clinical presentation of toxicity may include highly sensitive and specific signs for TCA poisoning on EKG, CNS effects including hallucinations, respiratory depression, seizures and coma. Peripheral effects include anti-cholinergic symptoms and predominance of hypotension (see detailed handout)

- Two TCA assays are offered at our lab. One for suspected TCA overdose (see below) and the other for therapeutic drug monitoring (currently unavailable and offered as a sendout; please consult detailed handout for indications and utility):

  - Semi-quantitative TCA immunoassay is offered 24 hours a day on a STAT basis in 2 steps. Initial screen on the Roche Modular Analyzer (EMIT) and confirmation of positive results on the semi-quantitative AxSYM (FPIA) with the following ranges

    - Less than 25 ng/ml
    - 0 – 300 ng/ml (therapeutic)
    - 300 – 500 ng/ml (signs of toxicity may arise)
    - 500 – 1000 ng/ml (more pronounced toxicity)
    - Greater than 1000 ng/ml

- **A major role of the Lab Resident is to communicate the relative reactivities for the suspected TCAs (please consult detailed handout for respective cross-reactivities; polyclonal antibody generated against desipramine)**

- Hydroxylated metabolites have variable cross-reactivities precluding the use of the assay to "follow down" the TCA level

- NO significant cross-reactivity with amoxopine, bupropion, loxapine, trazodone and fluoxetine

- There is cross-reactivity with the following medications: carbamazepine (Tegretol), diphenhydramine (Benadryl), cyclobenzaprine (Flexeril), cyproheptadine (Periactin), chlorpromazine (Thorazine) and perphenazine (Trilafon). *Therapeutic* dosages do NOT contribute significantly; however, *toxic* or *overdosed* levels of these medications may contribute significantly to the total reactivity usually in the range of 0 – 300 ng/ml if ingested without TCAs

- **The resident may choose to verbally report the TCA level to the nearest 100 ng/ml (e.g. 600-700 ng/ml) after cautioning of the large degree of variability of the assay(20-40%!)**

- **The resident should explain that serial TCA immunoassay levels are not warranted due to the semi-quantitative nature of the measurement, the high variability in the result and the cross reactivity with inactive metabolites and other medications.** However, a second determination, a few hours after the first, is appropriate to determine whether continued absorption is ongoing. Further levels may also be obtained to confirm a concentration below 300 ng/ml in order to qualify the patient for discharge only after sufficient time has elapsed to expect a concentration in this range

Alcohols and Glycols

- The commonly ingested alcohols and glycols include ethanol, methanol, isopropanol, ethylene glycol and propylene glycol (see detailed handout for availability)

- For most people intoxication begins at 50-150 mg/dl and health is threatened at levels above 500 mg/dl. However, some patients tolerate ethanol levels of 500 mg/dl

- Methanol is produced in very small amounts by normal metabolism and some naturally fermented alcoholic beverages. Levels of 1-5 mg/dl *may* not indicate a methanol overdose; obtain a follow-up value. Levels above 10 mg/dl are likely to develop some degree of delayed toxicity and hemodialysis is recommended for methanol concentrations above 25 mg/dl

- Any level of ethylene glycol is abnormal. Hemodialysis is recommended for levels above 25 mg/dl

- Isopropanol is much more intoxicating than ethanol but does not have the danger of delayed toxicity as is seen with methanol and ethylene glycol. Hemodialysis for isopropanol is not routine, but may become necessary for serum concentrations greater than 400 mg/dl

- Propylene glycol is often found in the serum of hospitalized patients at levels of 1-25 mg/dl from the diluent of injectable medications. Propylene glycol does not provide a risk for delayed toxicity and treatment is directed primarily at the initial intoxicating effects

- The intoxicating effects of alcohols are responsible for their initial toxicity. Longer chain alcohols are generally more intoxicating with isopropanol being the most potent and methanol the least. Ethylene glycol is more intoxicating than ethanol

- Methanol and ethylene glycol poisonings result in a more serious second phase of toxicity. Their metabolites cannot be integrated quickly into routine metabolic pathways. Accumulation of the toxic metabolites directly damages specific tissues and also contributes to the development of an anion gap metabolic acidosis. Indirectly, they raise the anion gap by producing lactic acidosis (true for other alcohols and glycols in large ingestions)

- **Methanol**: Initial intoxicating effects may be mild, although the delayed effects are severe. After a latent period of 10-24 hours, accumulation of formic acid produces an anion gap metabolic acidosis and the secondary lactic acidosis. Most consistent findings are visual disturbances, eventually leading to blindness. CNS symptoms commonly include inebriation, headache, dizziness, seizures and coma. Nausea, vomiting, meningismus, abdominal pain, obstipation and malaise are frequent complaints. Common laboratory findings are hypophosphatemia and an elevation of amylase and creatine kinase

- **Ethylene Glycol**: The anion gap metabolic acidosis which develops after 10-24 hours is the most severe for any of the alcohols. Specific signs and symptoms include unstable blood pressure, tachycardia, dysrhythmias, hyperventilation, pneumonitis and noncardiogenic pulmonary edema. Urinalysis reveals calcium oxalate or hippurate crystals in approximately 50% of cases. Acute tubular necrosis secondary to the deposition of oxalate crystals or the direct toxic effect of metabolites on the tubules occurs in 12 to 48 hours after ingestion. Hypocalcemia may occur during this phase and tetany may develop. A leukocytosis and CSF pleocytosis may be seen. Late findings (after 24 to 48 hours) may include complete cardiopulmonary failure and renal failure

- **Isopropanol**: Unlike the other alcohols, metabolism of isopropanol produces relatively non-toxic acetone, which is eliminated by renal and pulmonary excretion. Being the most

intoxicating alcohol, the initial CNS depressive effects of isopropanol ingestion represent its most serious toxicity. Whereas therapy of other alcohols may be characterized as preventing metabolism of the alcohol, for isopropanol the opposite is desired

- **Propylene Glycol**: Similar to isopropanol. Its metabolite, lactic acid, is incorporated into routine cellular physiology with only a small increase in circulating lactic acid unless massive amounts are ingested

- Blocking conversion of methanol and ethylene glycol into their toxic metabolites is achieved by ethanol (preferred) or fomepizole (4-methylpyrazole) administration. An optimal blood ethanol level of 100 to 150 mg/dl is necessary for efficacy. Patients are placed on an I.V. ethanol drip and frequent monitoring is required to assure that ethanol levels are within the therapeutic range, yet below toxicity

- Hemodialysis effectively eliminates all the alcohols and their circulating metabolites. Hemodialysis is recommended for methanol or ethylene glycol levels above 25 mg/dl. Hemodialysis occurs concurrent with ethanol or fomepizole therapy. Alcohol half-lives reduce to 3-4 hours with the combination of hemodialysis and blockade of alcohol dehydrogenase (see detailed handout for more comprehensive therapeutic management)

- Gas chromatography (GC) will separate the volatilized alcohols from serum or plasma, which are subsequently detected by flame ionization. Because of a significant difference in the volatility of the alcohols and the glycols, separate columns with different vaporization and running temperatures are required. An alcohol panel **(without detection of the glycols)** is a routine part of the serum/plasma overdose panel

- Glycol testing no longer requires approval of the laboratory medicine resident, although the resident is often informed when a test is requested in order to provide consultation (and is ALWAYS informed of any positive results). We frequently perform glycol testing on samples sent from other Connecticut hospitals. We are willing to provide this service 24 hours/day and the laboratory medicine resident is often involved for proper communication of the result to the referring clinicians

- **An important role of the laboratory medicine resident involved with a suspected (or confirmed) alcohol/glycol overdose is assistance with the measurement, calculation and interpretation of the osmolal gap. A misconception exists that an osmolal gap is expected after a toxic alcohol or glycol ingestion (see handout for case)**

- Serum osmolality should be measured by "freezing point depression". A common error is to utilize measurements from separate samples in calculating the osmolal gap. Use the following common formula for calculation: mOsm/kg = 2.0 Na (mmol/L) + BUN (mg/dL) ÷ 2.8 + Glucose (mg/dL) ÷ 18

- The "normal range" of the osmolal gap is often presented as < 10 mOsm/kg

- Lastly, a bedside test for the detection of antifreeze in urine may be employed. The procedure identifies fluorescein, an additive of antifreeze. A sample of the patient's urine is observed under an ultraviolet lamp. If fluorescein is present, then the urine will fluoresce or "glow" under the light

Barbiturates

Barbiturates are no longer commonly detected in the overdosed patient. Phenobarbital is still commonly prescribed as an anticonvulsant. A major goal of a barbiturate screen included within the overdose panel is to detect phenobarbital and to distinguish its presence from other barbiturates (given the difference in pharmacokinetics and reference ranges)

The shorter-acting barbiturates are taken up very rapidly by the brain and sleep is induced within a few circulation times. After that there is a slower redistribution phase when the drug is taken up by body fat and partitioned out of the CNS. Although the plasma half-life of these short-acting barbiturates is very short, their biological half-life (time in the body) is much longer as they are slowly removed from fatty tissue and metabolized by the liver. Renal excretion of short-acting barbiturates is minimal because plasma concentrations are kept very low. Reference ranges as well are very low

Long-acting barbiturates are also absorbed rapidly after an oral dose. However, they reach peak levels in the blood only after 8 to 12 hours and in the brain after 10 to 15 hours. They do not have a dominant second redistribution phase like the short-acting barbiturates. Instead, they are slowly metabolized by the liver with 25-30% excreted unchanged in the urine. The plasma half-lives of the long-acting barbiturates are equivalent to their biological half-lives and are very long

Short-acting: 1-3 µg/ml (therapeutic); 7 µg/ml (toxic)

Intermediate-acting: 1-5 µg/ml (therapeutic); 15 µg/ml (toxic)

Long-acting: 15-30 µg/ml (therapeutic); 45 µg/ml (toxic)

Toxicity of barbiturates is manifested by CNS depression. As toxicity becomes more severe, the degree of depression increases, patients may become unconscious or comatose. Severely poisoned patients may become anesthetized with total loss of neurologic function. Shock may occur due to medullary depression, peripheral vasodilation or impairment of myocardial contractility. Hypothermia and cutaneous bullae are also sometimes noted (see handout for detailed therapeutic management)

Test 1, "Barbiturate Overdose Screen": A non-specific immunoassay on the Roche Modular Analyzer detects all barbiturates present at potentially *toxic* concentrations. Note that a barbiturate may be present at a therapeutic concentration but reported as negative: "not present at toxic concentrations" (consult handout for lower limits of detection). Note that the non-specific, screening immunoassay cannot be employed for quantitation because of variable reactivity with different barbiturates

Test 2, "Phenobarbital Quantitation": For the purposes of therapeutic drug monitoring, an immunoassay is available which is highly specific for phenobarbital on the Roche Modular Analyzer. The lower limit of detection for this assay is 1 µg/ml of Phenobarbital (may be ordered separately)

Test 3, "Total Barbiturate Quantitation": The "total" quantitation of all barbiturates can be achieved using UV/Vis spectrophotometry. The lower limit of detection for this assay is 2 µg/ml of total barbiturate (may be ordered separately)

Some clinicians may be confused about the report of barbiturates "not present at toxic concentrations" in the overdose panel; it is important to communicate the minimal detection limits for the relevant barbiturates in the screening immunoassay and also recommend use of the 2nd and 3rd tests for quantitation, if clinically indicated