

ICU CORNER

High-yield toxicology: Essential facts for the critical care boards

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GENERAL INFORMATION

Key points: (a) It is imperative that critical care practitioners are familiar with the most commonly encountered types of poisoning and toxicity – early recognition and appropriate intervention are crucial when approaching patients affected by toxins and poisons; (b) Acetaminophen toxicity has four distinct stages, predictable toxicity within 4 to 24 hours of exposure, and can be treated with N-acetylcysteine administration; (c) Anticholinergic toxicity is associated with characteristic signs and symptoms, including hyperthermia, dry skin, flushing, mydriasis and delirium; (d) Cyanide poisoning can be rapidly fatal – early recognition and treatment with thiosulfate, hydroxycobalamin, or amyl nitrate are essential; (e) Digitalis toxicity is associated with either increased drug level or increased sensitivity to the drug, and can produce a variety of symptoms (mostly non-specific) – cardiac arrhythmias constitute the most common cause of mortality; (f) Lithium toxicity can result in severe neurologic and cardiovascular symptoms – dialysis may be indicated in cases of severe toxicity or concurrent renal failure; (g) Organophosphate poisoning is characterized by muscarinic side effects, nicotinic side effects and central nervous system toxicity – muscarinic symptoms seen in acute organophosphate poisoning can be remembered by the use of the mnemonic DUMBELS (defecation, urination, miosis, bronchorrhea, bronchospasm, bradycardia, emesis, lacrimation, and salivation).

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ACETAMINOPHEN TOXICITY

Acetaminophen toxicity may occur following acute ingestion of more than 140 mg/kg, or when more than 7.5 grams are ingested during a 24-hour period by an adult. The diagnosis of acetaminophen toxicity initially depends on laboratory testing because symptoms may be absent or non-specific at first. Due to potentially devastating consequences of delay in diagnosis, acetaminophen level should be measured in all patients with any drug overdose as acetaminophen is commonly co-ingested.

Acetaminophen toxicity presents in four stages: (a) during the first day, symptoms may be absent or nonspecific – nausea, vomiting, malaise, and anorexia; (b) on days 2-3, nausea and vomiting improve, but signs and symptoms of hepatotoxicity appear – right upper quadrant pain and tenderness, elevations in bilirubin and transaminases; (c) on days 3-4, progression to fulminant hepatic failure may occur, with lactic acidosis, renal failure, encephalopathy, coagulopathy, and recurrent nausea/vomiting; (d) patients who survive the initial toxicity enter the recovery phase, which is characterized by recovery from hepatic failure over a period of weeks with complete resolution of hepatic dysfunction.

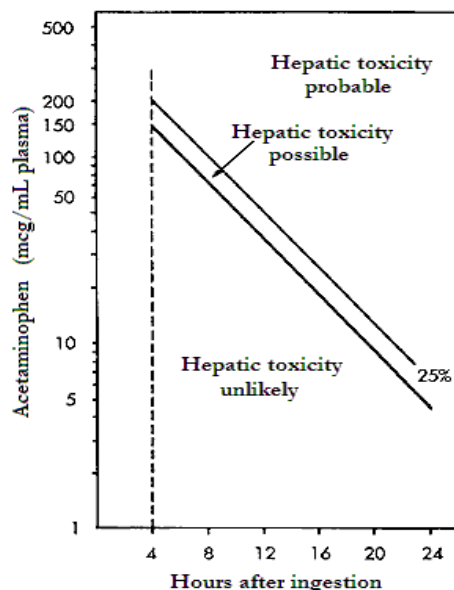


Figure 1. The Rumack-Matthew nomogram accurately predicts acetaminophen toxicity based on the serum acetaminophen level measured 4 to 24 hours after the estimated time of ingestion. Outside of this 'time window' the nomogram is not reliable.

In a single large overdose, the Rumack-Matthew nomogram (**Figure 1**) accurately predicts acetaminophen toxicity based on the serum acetaminophen level measured 4 to 24 hours after the estimated time of ingestion. The nomogram is not useful outside of this time range. When multiple ingestions have occurred over a period of time, assessment is more difficult. One approach is to assume single ingestion and use the Rumack-Matthew nomogram.

The differential diagnosis of acute acetaminophen toxicity includes hepatitis (viral versus alcoholic), ingestion of other drugs or toxins, and a number of hepatobiliary disorders. Acute acetaminophen poisoning can often be differentiated from other forms of hepatitis by its acute onset, rapid progression, and markedly elevated transaminase enzyme levels.

Evaluation and treatment of acetaminophen toxicity includes: (a) assurance of adequate respiratory and circulatory status; (b) acetaminophen level drawn early – optimally 4 to 24 hours after ingestion; (c) other laboratory values – hepatic function panel, coagulation profile, comprehensive blood count, electrolytes, glucose, blood urea nitrogen, and creatinine; (d) activated charcoal 1 gram/kg is indicated for gastrointestinal decontamination in cases of co-ingestions; (e) N-acetylcysteine administration; (f) appropriate level of care, including the ICU, for close clinical observation; and (g) hepatic transplantation for cases of overwhelming toxicity with delay in treatment – these patients may also require correction of coagulopathy/acidosis and treatment of cerebral edema.

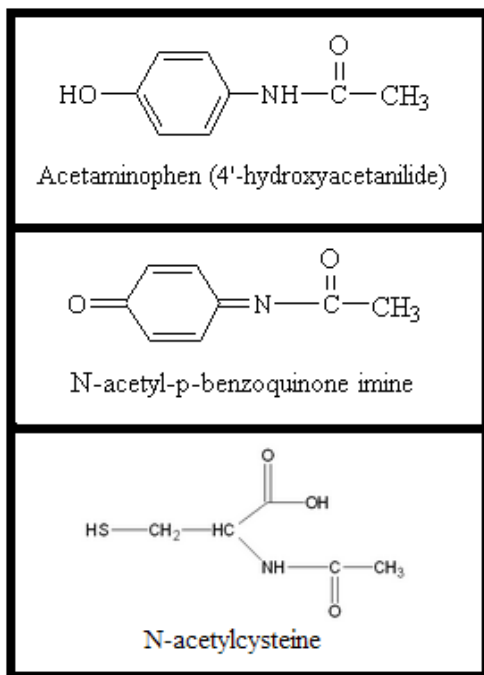


Figure 2. Metabolites involved in acetaminophen toxicity and its treatment. Top – acetaminophen; Middle – N-acetyl-p-benzoquinone imine (toxic metabolite); Bottom – N-acetylcysteine (antidote).

N-acetylcysteine is the specific antidote for acetaminophen toxicity. It is given orally or via nasogastric tube as a 140 mg/kg loading dose followed by administration of 70 mg/kg every 4 hours for a total of 17 doses. It is effective in preventing toxicity if given within 8 hours and significantly reduces hepatotoxicity if given within 24 hours of ingestion. Nausea and/or vomiting associated with N-acetylcysteine can be alleviated by administering antiemetic agents. See **Figure 3** for more detailed depiction of the metabolic steps involved in acetaminophen toxicity and N-acetylcysteine action.

ANTICHOLINERGIC TOXICITY

Anticholinergic toxicity is defined as clinical syndrome resulting from blocking the effects of acetylcholine at the muscarinic receptor. Causative agents include: (a) anticholinergic medications; (b) antihistamines; (c) tricyclic antidepressants; (d) chemical warfare agents – 3-quinuclidinyl benzilate (QNB or BZ); (e) ingestion of *Atropa belladonna*, Jimson weed, *Amanita*

muscaria mushrooms; and (f) parasympatholytic medications – atropine, scopolamine, hyoscyamine.

Symptoms of anticholinergic toxicity include: (a) hyperthermia; (b) dry skin; (c) flushing; (d) mydriasis; and (e) delirium. There is a convenient mnemonic for this type of toxicity – **Hot** as a hare, **dry** as a bone, **red** as a beet, **blind** as a bat, **mad** as a hatter.

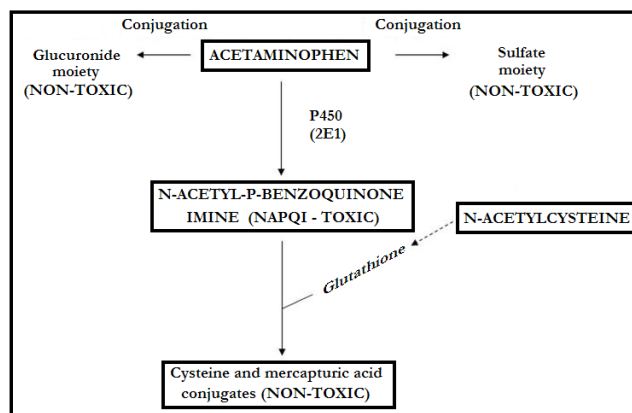


Figure 3. Metabolic steps and metabolites involved in acetaminophen toxicity. At high doses, the liver generates a highly reactive metabolite, N-acetyl-p-benzoquinone, which interacts with nucleophilic portions of critical hepatocyte protein.

Complete list of symptoms may also include: (a) seizures; (b) tachycardia; (c) hypertension; (d) dry mouth; (e) blurred vision; (f) decreased bowel sounds; (g) constipation; (h) urinary retention; (i) peripheral vasodilation; and (j) altered level of consciousness – hallucinations, incoherent speech, delirium, coma.

Management of anticholinergic toxicity includes: (a) supportive measures – including protecting the patient from injuring self, close cardio-respiratory monitoring, and intubation for respiratory compromise; (b) gastric lavage ± administration of activated charcoal for ingestions; (c) control of hyperthermia; (d) potential use of physostigmine as an antidote – usually not recommended (may precipitate seizures and cardiac arrest in the setting tricyclic antidepressant overdose); and (e) diazepam use as indicated in the setting of seizures/agitation.

CYANIDE POISONING

Cyanide is a naturally occurring potent cellular toxin. Acute cyanide toxicity results from: (a) accidental occupational exposures; (b) accidental or suicidal exposure to substances converted to cyanide (vinyl, polyurethane, wool, silk); (c) ingestion of plants or foods containing natural cyanogenic glycosides; and (d) iatrogenic toxicity during prolonged nitroprusside administration.

The reported average lethal dose of cyanide taken orally varies from 40 to 100 mg in an average adult. Inhalation of air containing approximately 100 ppm of cyanide can be fatal in 30 to 60 minutes. At a concentration of 300 ppm, death occurs within minutes. Therefore, prompt recognition of cyanide poisoning and administration of appropriate treatment are essential.

Cyanide effectively and rapidly halts mitochondrial oxidative phosphorylation by binding the ferric ion (Fe^{3+}) of cytochrome oxidase a_3 . Affected cells cannot utilize oxygen for aerobic

respiration, resulting in life-threatening high anion-gap lactic acidosis. Cyanide also binds the ferrous (Fe^{2+}) ion of hemoglobin to create cyanohemoglobin, which is unable to transport oxygen. Cellular toxicity is further potentiated by oxygen free radicals produced by the inhibition of various antioxidants. Cyanide also reduces seizure threshold by inhibiting the formation of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. Cyanide exerts its effects on virtually every body system. Despite respiratory and cardiac failure, the patient with cyanide poisoning does not appear cyanotic due to the body's inability to utilize oxygen at the tissue level and resulting increases in venous oxygenation.

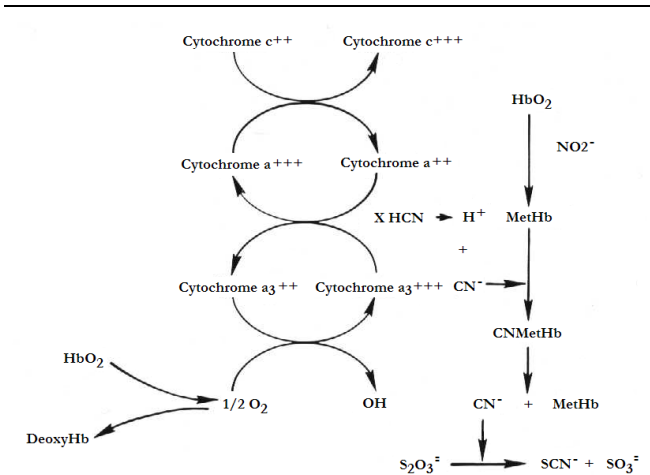


Figure 4. Proposed mechanism of cyanide toxicity. Hydrogen cyanide appears to block electron transfer in the cytochrome a₃ complex. As a consequence, oxygen utilization is decreased and oxidative metabolism may slow to the point where tissue metabolic demands are no longer met. In the brain stem nuclei, this effect may result in central respiratory arrest and death. After injection of sodium nitrite, methemoglobin is generated, which can compete with cytochrome a₃ for free cyanide. The injection of thiosulfate provides substrate for the enzyme, rhodanese, which catalyzes the conversion of cyanide to thiosulfate.

Laboratory determination of cyanide levels usually takes too long, which makes obtaining these levels impractical in the acute setting. However, cyanide levels may be useful as a confirmatory test. High lactate levels tend to be significantly associated with cyanide poisoning and can be used to direct resuscitation. Arterial blood gases and CO-oximetry may help diagnose carbon monoxide poisoning, which can have clinical manifestations similar to those of cyanide toxicity and may be present concurrently following inhalation injury.

Treatment of cyanide poisoning needs to be initiated based on clinical history, physical examination findings and high index of suspicion. Aggressive supportive therapy should be instituted immediately. Decontamination is an important component of therapy for cyanide toxicity. Given the various routes of potential exposure, care must be taken to avoid endangering the provider. The patient's clothing must be removed and wounds must be cleaned. Gastrointestinal decontamination can be performed with activated charcoal. In cases of nitroprusside toxicity (**Figure 5**) the infusion should be stopped immediately.

Antidotes to cyanide serve mainly to augment the body's natural protective metabolic mechanisms (**Figures 4 and 5**). The majority

of cyanide metabolism involves the addition of sulfur to the cyanide molecule in order to form thiocyanate. This reaction is facilitated by the enzyme rhodanese. Cyanide also combines with hydroxycobalamin to form cyanocobalamin (vitamin B₁₂). Both thiocyanate and cyanocobalamin are excreted in the urine.

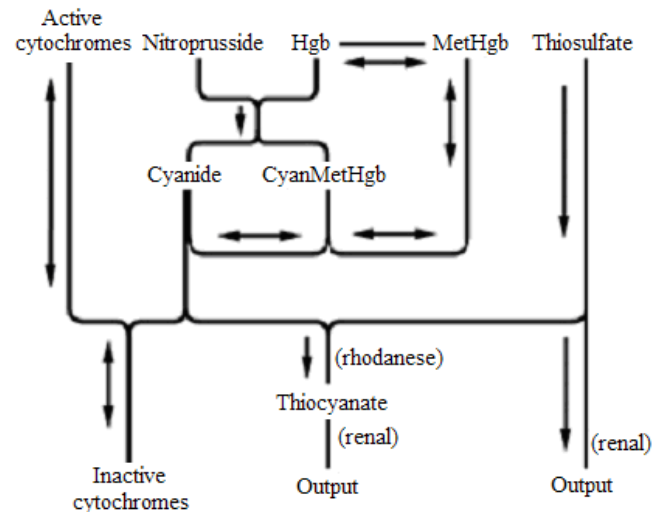


Figure 5. Metabolism of sodium nitroprusside and its relationship to cyanide production.

One antidotal strategy involves the administration sulfur (12.5 grams of intravenous sodium thiosulfate) to act as substrate in the rhodanese reaction to form thiocyanate. Another strategy is to give hydroxycobalamin (50 mg/kg for most adult patients) intravenously to bind cyanide directly. Yet another strategy is to make the iron in the hemoglobin molecule a more attractive binding site for the cyanide and release it from cytochrome oxidase. The administration of amyl nitrite, sodium nitrite, or dimethylaminophenol to form methemoglobin oxidizes iron from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) form. Methemoglobin then binds cyanide to form cyanomethemoglobin, which is somewhat less toxic. Methemoglobinemia of 20-30% is the goal of treatment for the average adult, but may be lethal in the pediatric or anemic patient. Amyl nitrite is inhaled, short-lived, results in only 5% methemoglobinemia, and is suitable only as a temporizing measure. Intravenous sodium nitrite (300 mg) results in up to 25% methemoglobinemia and is the treatment of choice for the average adult patient exposed to cyanide.

DIGITALIS TOXICITY

Digitalis (cardiac glycoside) intoxication is most often associated with chronic therapy, although approximately 10% is caused by an acute accidental overdose and up to 40% is caused by acute intentional overdose during suicide attempt. Deleterious effects of digitalis are associated with either increased drug levels or increased sensitivity to the drug. Increased drug levels are commonly associated with renal insufficiency, where digitalis accumulation is due to impaired excretion. Sensitivity to digoxin is augmented by advanced age, cardiac disease, various electrolyte disturbances. When taken concurrently, quinidine, cyclosporine, verapamil, diltiazem, tetracycline, erythromycin, paroxetine, and rifampin are all known to predispose to digitalis toxicity. Plasma

levels of digoxin do not necessarily predict toxicity, but can be used to guide dosing and monitor response to therapy.

Cardiac glycosides impart their therapeutic effect by inhibiting the $\text{Na}^+\text{-K}^+$ ATPase pump (Figure 6). The resulting increase in intracellular sodium impairs transport of calcium out of the cell by a separate mechanism. Physiologically, the net effect is an increase in cardiac contractility. Digitalis also decreases conduction through the AV and SA nodes, and increases automaticity of cardiac myocytes. Digitalis tends to accumulate in skeletal muscle (toxicity may be affected more by lean body weight than actual body weight).

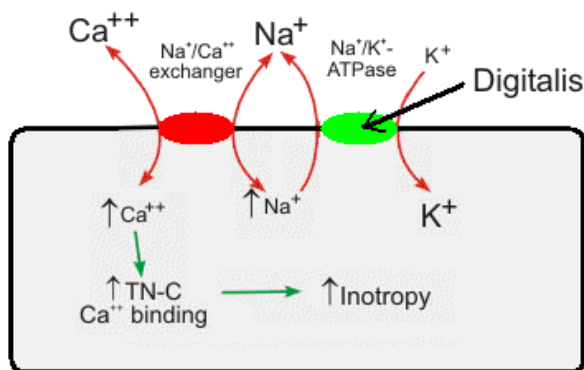


Figure 6. Cellular mechanism of cardiac glycoside action (TN-C = troponin).

Effects of cardiac glycoside toxicity are largely non-specific and include fatigue, visual changes, gastrointestinal distress, and other neurologic symptoms. Electrophysiologic changes are more specific. These include: (a) ventricular ectopy (earliest sign); (b) atrial tachyarrhythmias (from increased automaticity); (c) and high degree heart block (from decreased conduction). Cardiac arrhythmias are the usual cause of death in cases of fatal digitalis toxicity.

Potassium level is an important consideration in the setting of digoxin toxicity, depending on whether the overexposure to digitalis is acute or chronic. Hyperkalemia in acute toxicity is associated with high mortality. Potassium levels greater than 5.5 mEq/dL concurrent to digoxin poisoning are associated with a significantly higher mortality (over 90%) than potassium less than 5.0 mEq/dL (mortality less than 10%). Hypokalemia can potentiate chronic digoxin toxicity and warrants prompt correction.

In terms of therapy, symptomatic bradycardia should be treated with atropine. Transvenous pacing and beta-agonists should be avoided due to the potential risk of more serious arrhythmias. Hemodynamic instability should prompt the use of digoxin-specific F_{ab} fragments (Digibind). Gastrointestinal decontamination with activated charcoal is indicated if ingestion has occurred within six to eight hours. Calcium should not be given when correcting serum potassium due to the possibility of worsening intracellular hypercalcemia. Other life-threatening symptoms or electrophysiologic derangements should prompt the treatment with digoxin-specific F_{ab} fragments, which rapidly bind extracellular digoxin. The F_{ab} -bound digoxin is unable to inhibit $\text{Na}^+\text{-K}^+$ ATPase and undergoes rapid renal excretion.

LITHIUM TOXICITY

Most cases of lithium poisoning are due to unintentional overdose during chronic therapy, and are often associated with concurrent volume depletion and renal insufficiency. However, acute intentional overdose is not uncommon.

Lithium is rapidly absorbed from the gastrointestinal tract and is eliminated by glomerular filtration (80% reabsorption in tubules). Lithium is a very small molecule and has virtually no protein binding and a low volume of distribution. Lithium has a narrow therapeutic index, and the therapeutic concentration is usually 0.6-1.2 mEq/L. Elimination half-life of lithium is approximately 18 hours, but is longer in the elderly and patients on chronic therapy.

There are multiple clinical features of lithium poisoning. Serum levels following acute ingestion correlate rather poorly with intracellular concentrations and clinical symptoms. Severe toxicity may occur at lower serum concentrations in chronic ingestion than in acute overdose. Also, intracellular concentrations may better correlate with serum concentrations in chronic and acute-on-chronic toxicity.

Mild intoxication (serum lithium 1.5-2.5 mEq/L) is characterized by: (a) tremors; (b) ataxia; (c) nystagmus; (d) choreoathetosis; (e) photophobia; and (f) lethargy. **Moderate intoxication** (serum lithium 2.5-3.5 mEq/L) can be associated with: (a) agitation; (b) fasciculations; (c) confusion; (d) cerebellar signs; and (e) nausea, vomiting, diarrhea. **Severe toxicity** (serum level >3.5 mEq/L) is associated with: (a) seizures; (b) coma; (c) cardiovascular effects – sinus bradycardia, hypotension, non-specific ST segment changes on ECG; and (d) decreased anion gap (< 5 mEq/L). Severe poisoning may result in permanent neurologic deficits in up to 10% of patients. **Chronic toxicity** may manifest with nephrogenic diabetes insipidus, renal failure, hypothyroidism, and leukocytosis.

Treatment of lithium toxicity involves: (a) general supportive measures – including hemodynamic monitoring and airway maintenance as indicated; (b) gastric lavage early after an acute overdose; (c) whole bowel irrigation may be useful to reduce the absorption of sustained-release lithium preparations; (d) meticulous fluid/electrolyte management; and (e) renal replacement therapy as indicated. Activated charcoal does not bind to lithium well and has no role in single-agent lithium poisoning.

Hemodialysis and hemofiltration is indicated: (a) for serum levels >3.5 mEq/L in acute ingestion; (b) serum levels >2.5 mEq/L in chronic ingestion, symptomatic patients or patients with renal insufficiency; (c) serum level 1.5-2.5 mEq/L in any patient with renal insufficiency, severe neurological symptoms or unstable hemodynamics; and (d) serum level <1.5 mEq/L in patients with end-stage renal failure or following large ingestion with expected subsequent rise in serum lithium levels.

Hemodialysis is more effective than hemofiltration. Problems with rebound lithium toxicity after discontinuation of hemodialysis (due to tissue redistribution of the drug) can be remedied by extending the dialysis session to 8-12 hours or by initiating continuous renal replacement therapy.

ORGANOPHOSPHATE POISONING

Organophosphate poisoning occurs after exposure (ingestion, skin contact, inhalation, eye contact, parenteral exposure) to

organophosphorus pesticides including methyl parathion, diazinon, and dichlorovos, among others. It can also occur after exposure to organophosphate chemical warfare agents – GA, GB, and VX. Organophosphorus agents act acutely by inhibiting acetylcholinesterase in the nervous system with subsequent accumulation of toxic levels of acetylcholine. They may also inhibit butylcholinesterases and other esterases. The function of butylcholinesterase is unknown, but its inhibition can be used to support/confirm the suspicion of exposure to an organophosphate. In many cases, the organophosphorylated enzyme is fairly stable, and recovery from intoxication may be slow. Reactivation of inhibited enzyme may occur spontaneously – rates of reactivation depending on the tissue as well as on the chemical group attached to the enzyme.

Signs and symptoms of organophosphorus poisoning can be divided into three major groups: (a) muscarinic side effects; (b) nicotinic side effects; and (c) central nervous system (CNS) toxicity. Some effects may be more prominent than others and their timing may differ.

Muscarinic effects include: (a) increased bronchial secretions; (b) excessive sweating; (c) salivation and lacrimation; (d) pinpoint pupils; (e) bronchoconstriction; (f) abdominal cramps with vomiting and diarrhea; and (g) bradycardia.

Nicotinic effects include: (a) muscle fasciculation; (b) paralysis of the diaphragm and respiratory muscles in severe cases; as well as (c) tachycardia and hypertension. Nicotinic effects are analogous to the depolarizing effects of succinylcholine.

Central nervous system effects include: (a) headaches; (b) dizziness; (c) restlessness and anxiety; (d) confusion; (e) convulsions and coma in severe cases; as well as (f) depression of the respiratory and vasomotor centers.

Three specific syndromes are associated with organophosphate poisoning. They include: (a) acute toxicity; (b) intermediate syndrome; and (c) chronic syndrome. These syndromes are described below.

Acute toxicity. The muscarinic symptoms associated with acute organophosphate toxicity can be remembered by the use of two alternative mnemonics: (a) DUMBELS – defecation, urination, miosis, bronchorrhea/bronchospasm/bradycardia, emesis, lacrimation, and salivation; and (b) SLUDGE/BBB – salivation, lacrimation, urination, defecation, gastric emesis, bronchorrhea/bronchospasm/bradycardia. However, it is important to remember that these mnemonics do not account for the CNS and nicotinic side effects of organophosphates.

Intermediate syndrome. This syndrome occurs 24 to 96 hours after organophosphate exposure. Bulbar, respiratory, and proximal muscle weakness constitute the most prominent complaints, but usually resolve within 1-3 weeks. The intermediate syndrome may feature muscle paralysis following the acute cholinergic phase, and arises between the period of early cholinergic syndrome and

the late-onset peripheral neuropathy (see below).

Chronic syndrome. This syndrome is also known as organophosphorus agent-induced delayed peripheral neuropathy. This can be usually seen several weeks after exposure, with primarily motor involvement. The chronic syndrome may resolve spontaneously, but permanent neurological dysfunction can occur at times.

Diagnosis. History of known ingestion, inhalation, or other contact is very important. Organophosphate poisoning can be diagnosed with the help of the following clinical findings and maneuvers: (a) many organophosphorus agents have petroleum or garlic-like odor; (b) atropine challenge (1 mg of atropine in adults or 0.01 to 0.02 mg/kg in children) with the absence of anticholinergic effects strongly suggests the diagnosis of organophosphate poisoning; (c) chemical analysis of vomitus or gastric aspirate; and (d) direct measurement of RBC acetylcholinesterase activity allows for measurement of the degree of toxicity.

Treatment of acute toxicity. Adequate oxygenation should be maintained, including mechanical ventilation as indicated. In organophosphate poisoning, death is often due to respiratory arrest, which infrequently occurs insidiously. Benzodiazepines can be utilized if seizures occur.

Decontamination may be useful in cases of topical skin exposure – all affected areas should be aggressively irrigated following removal of clothing. In cases of ingestion, emptying the stomach via gastric lavage is most beneficial within 1-2 hours of exposure. Activated charcoal may be effective for organophosphorus pesticides.

Atropine can be given as intravenous bolus (2-5 mg in adult or 0.05 mg/kg in children). The dose can be escalated every 3-5 minutes until bronchial secretions or wheezing stop. Atropine infusion is then started by setting the hourly infusion dose at 20% to 30% of the total amount of atropine required to stabilize the patient initially. The infusion is then maintained for 2-3 days, followed by 25% to 33% daily dose reductions.

Pralidoxime therapy may be used in patients with signs and symptoms of cholinergic toxicity following organophosphorus poisoning. Pralidoxime is recommended for poisoning due to carbamate (reversible inhibitor of acetylcholinesterase). The recommended dose is 2 grams in adults (25-50 mg/kg in children) intravenously over 30 minutes, followed by a continuous infusion at 8 mg/kg/hour in adults (10-20 mg/kg/hour in children).

Maintenance of proper fluid and electrolyte balance is extremely important in the setting of organophosphate poisoning. Patients may require significant amounts of fluid and electrolyte replacement secondary to losses due to vomiting, diarrhea, high fever, and decreased or absent oral intake.

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