Clinical Toxicology

Introduction
Management of the Poisoned Patient

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Clinical Toxicology

The branch of toxicology that is concerned with human poisoning:-

- Drug over doses
- Pharmaceutical
- Drugs of abuse

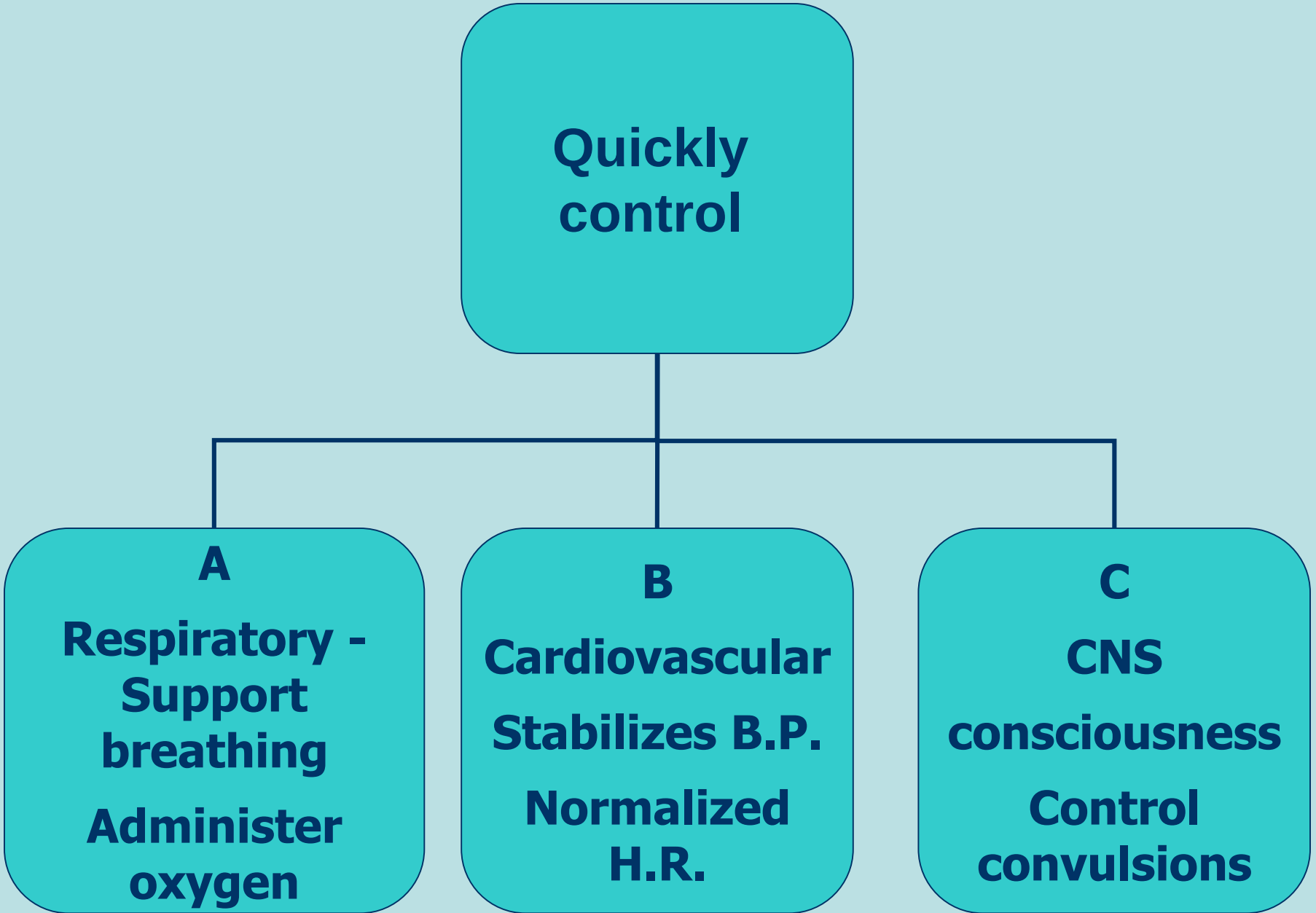
- Toxic exposures
- Environmental
- Occupational
- Accidental

Clinical Toxicology

Is the study of the abnormalities associated with short-term & long-term exposure to various toxic chemicals.

It compatible with other sciences such as biochemistry, pharmacology, & pathology.

General non-specific assessments



Case study: What are the first steps involved in the management of the following case?

A 21 year old man admitted to the emergency department (ED) at Al-Kindy teaching hospital suffering from difficulty in breathing after exposing to lachrymator gas.

Lachrymator gas: A chemical weapon that causes sever eye lacrymation and respiratory pain, skin irritation, bleeding and even blindness

Clinical strategy for treatment of the poisoned patient

The following general steps represent important components of the initial clinical encounter with a poisoned patient:

1. Stabilization of the patient
2. Clinical evaluation (history, physical, laboratory, & radiology…ect)
3. Prevention of further toxin absorption
4. Enhancement of toxin elimination
5. Administration of antidote
6. Supportive care & clinical follow-up

1- Clinical Stabilization

The first priority in the treatment of the poisoned patient is stabilization. Assessment of the vital signs and the effectiveness of respiration and circulation are the initial concerns. Some toxins or drugs can cause seizures early in the course of presentation. The steps and clinical procedures incorporated to stabilize a poisoned patient are numerous and include:

1- support of ventilation,

2- circulation,

3- oxygenation.

In critically ill patients, sometimes treatment interventions must be initiated before a patient is truly stable.

2-Clinical evaluation

- **A) Clinical History**
- The primary goal of taking a medical history in poisoned patients is to determine, if possible, the substance ingested or the substance to which the patient has been exposed as well as the extent and time of exposure.
- Information sources commonly employed in this setting include:
  - family members,
  - emergency medical technicians who were at the division,
  - a pharmacist who can sometimes provide a listing of prescriptions recently filled,
  - an employer who can disclose what chemicals are available in the work environment.

What are the importance of clinical History?

- With an estimate of dose, the toxicologist can refer to various information sources to determine what the range of expected clinical effects might be from the exposure.
- The estimation of expected toxicity greatly assists with the treatment of poisoned patients.
- Estimating the timing of the exposure to the poison is frequently the most difficult aspect of the clinical history in the setting of treatment of the poisoned patient.
- Accurate identification of ingestants is particularly important in the patient exposed to agents that have delayed onset of toxic effects, such as acetonitrile (which is metabolized to cyanide), or MAOIs.

B-Physical examination

-Its called in case of toxicity " Toxidrome " mean symptom.
This help to suggest what kind of poisoning is ingested.

- Categorization of patient's presentation into toxic syndromes allows for the initiation of rational treatment based on the most likely category of toxin responsible, even if the nature of the toxin is unknown.

Most common toxidrome

1- Cholinergic toxidrome

Sign & symptom of cholinergic drugs
Example organophosphorous (pesticide) that causes SLUDGE
S= salivation
L= lacrimation
U= urination
D= diaphoresis
G= gastero-intestinal sound
E= emesis

Physical examination

On CNS causes

- Confusion
- CNS depression
- Seizure
- Agitation
- Delirium

On eye causes

- Miosis

On blood vessel & CVS causes

- Hypertension
- Tachycardia

At the end = tremor & coma.

Examples: mushroom, organophosphorous, carbamate (neostigmin & physiostigmin)

Physical examination

2-Non Cholinergic toxidrome

Sign & symptom

- Urinary retention
- Dry mouth
- Flushing
- Decreased in bowel sound
- Mydriasis
- Increased in body temp.
- Tachycardia
- Coma

Example: antihistamine, smooth muscle relaxant, TCA, antipsychotic drugs.

Physical examination

3-Benzodiazepine toxidrome

- Cause sedation & hypnotic, & loss of CNS function
- High doses of benzodiazepine may lead to coma, confusion & apnea.

❖ Drugs that cause the same effect:

- Ethanol, methanol, barbiturate, anticonvulsant & TCA

4-Sympathomimetics toxidrome

- Hyperpyrexia
- Diaphoresis
- Mydriasis
- Seizure
- Hypertension
- Tachycardia

Physical examination

5-Opiate toxidrome

- Miosis
- Decreased in bowel sound
- Hypothermia
- Hypotension
- Respiratory depression in sever dose
- Bradycardia
- Alter mental state

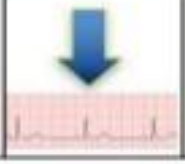
Example:

Heroin, morphine, codeine, & any synthetic & semisynthetic opiate.

6-Hallucination toxidrome

- Impair judgment
- Panic reaction
- Depression

Example: cocaine, amphetamine & phencyclidine

	HR & BP	Resp.	Temperature	Pupils	Bowel Sounds	Diaphoresis
Anticholinergic **Anticholinergics** –Atropine, scopolamine, glycopyrrolate benztropine, trihexyphenidyl **Antihistamines** – Chlorpheniramine, Cyproheptadine, Doxylamine, Hydroxyzine, Dimenhydrinate, Diphenhydramine, Meclizine Promethazine		No change		Dilated		
Cholinergic Organic Phosphorous Compounds: Carbamates • Arecholine, Pilocarpine, Urecholine (Betanechol), Carbachol, Choline, Metacholine, Mushrooms	No change	No change	No change	Pinpoint		
Opioid Morphine • Codeine • Tramadol • Heroin • Meperidine • Diphenoxylate • Hydromorphone • Fentanyl • Methadone • Propoxyphene • Pentazocine • DXM • Oxycodone • Hydrocodone				Pinpoint		
Sympathomimetic Caffeine, cocaine, amphetamines, methamphetamines, Ritalin, LSD, Theophylline, MDMA				Dilated		
Sedative-Hypnotic anti-anxiety agents, muscle relaxants, antiepileptics and preanesthetic medications –Barbituates –Benzodiazepines				No change		

C-Laboratory evaluation

- Because of the limited clinical availability of " diagnostic " laboratory tests for poisons, toxicologist utilize specific, routinely obtained clinical laboratory data which are:

1-Anion gap
2-Osmol gap
To determine what poisons may have been ingested.

Anion gap

Is calculated as the difference between the serum Na ion conc. & the sum of the serum Cl & HCO3 ion conc.
A normal anion gap is < 12.
When there is laboratory evidence of metabolic acidosis, the finding of an elevated anion gap would suggest systemic toxicity from a relatively limited number of agents.

Laboratory evaluation

A	Alcohol(ethanol ketoacidosis)
T	Toluene
M	Methanol
U	Uremia
D	Diabetic ketoacidosis
P	Paraldehyde
I	Iron, isoniazid
L	Lactic acid
E	Ethylene glycol
S	Salicylate

Laboratory evaluation

Osmol gap

Is calculated as the numerical difference between the measured serum osmolarity and the serum osmolarity calculated from the clinical chemistry measurements of the serum sodium ion, glucose & blood urea nitrogen (BUN) concentration.

The normal osmol gap is < 10 mOsm.

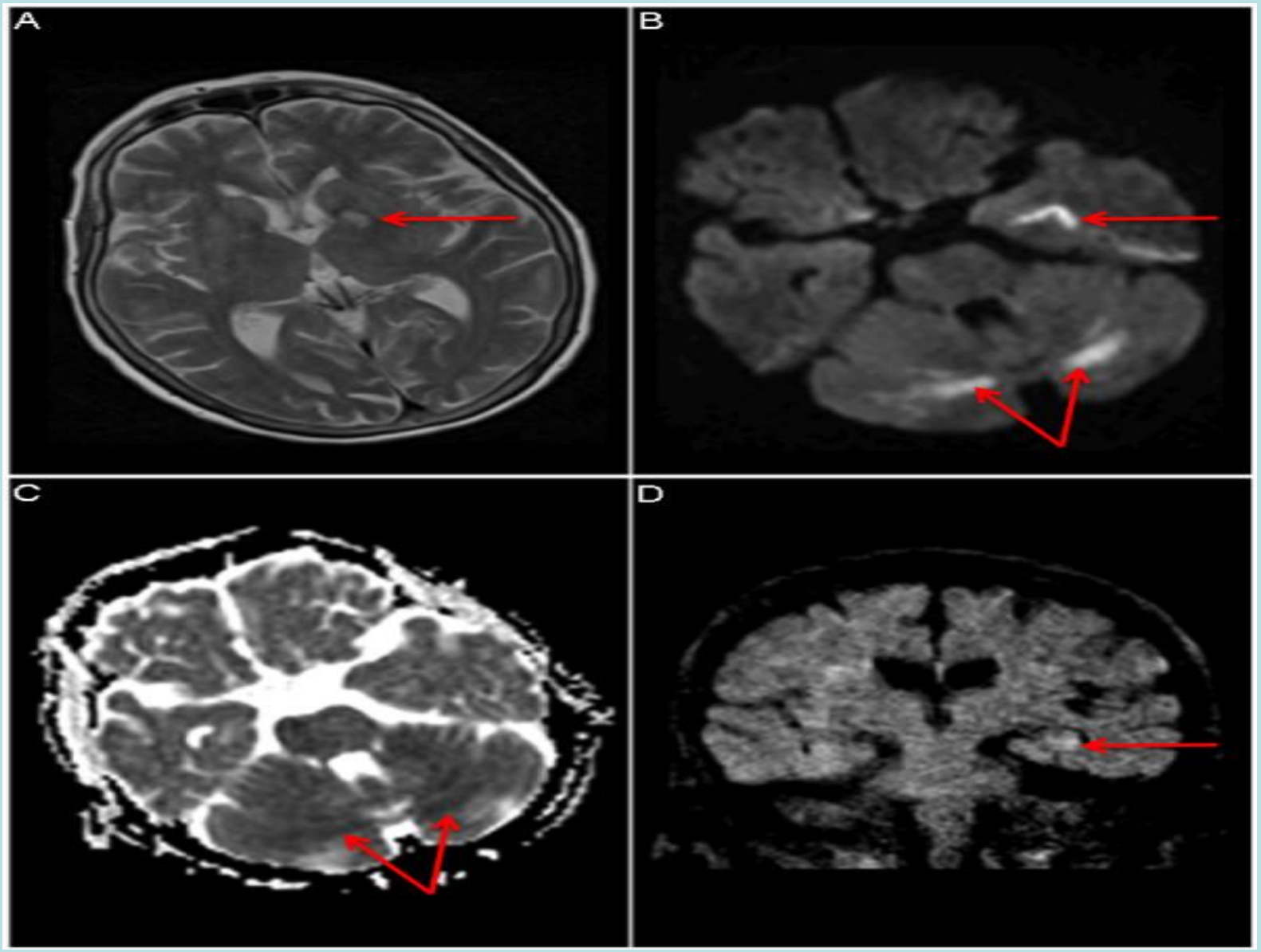
An elevated osmol gap suggests the presence of an osmotically active substance (methanol, ethanol, ethylene glycol, & isopropanol) in the plasma that is not accounted for by the sodium ion, glucose, or BUN conc.

Calculated osmolarity = (2 x [Na+]) + [glucose] + [urea])

Osmolar gap = Osmolality (measured) – Osmolarity (calculated)

D-Radiographic Examination

- The use of clinical radiographs to visualize drug overdose or poison ingestions is relatively limited.
- Plain radiographs can detect a significant amount of ingested oral medication containing ferrous or potassium salts.
- Certain formulations that have an enteric coating or certain types of sustained release products are radiopaque as well.
- Plain radiography & other types of diagnostic imaging in clinical toxicology can also be extremely valuable for the diagnosis of toxin-induced pathology.
  - For example, the detection of drug-induced non-cardiac pulmonary edema is associated with serious intoxication with salicylates & opioid agonists.
  - Significant exposure to carbon monoxide (CO) has been associated with CT and/or MRI lesions of the brain consisting of low-density areas in the cerebral white matter & in the basal ganglia.


A
B
C
D

3-Prevention of further toxin absorption

1- Dilution

The clinical procedure often recommended whenever ingestion of poison suspected, is dilution with water.
The recommended amount is 1-2 cup full for a child & 2-3 cup full for adult.
Excessive liquid may distend the stomach wall causing premature evacuation of its content into the intestine.

Advantage of dilution with water:
1- Reduce gastric irritation
2- Add bulk to the stomach that may be needed for emesis.
Nothing should be administered orally to an unconscious patient or if the gag reflex is absent & in cases of ingestion of solid dosage forms such as tablets or capsules because dilution can promote dissolution & absorption of the medication.

Prevention of further toxin absorption

2- Emesis

It is the induction of vomiting to get rid of stomach content, so emetic agent decreases amount of poison inside the stomach so decreases its absorption.

This can be done by:

A- Mechanical emesis: by putting a spoon or finger at the end of the tongue.

B- Chemically induced emesis: by syrup of ipecac, or apomorphine, or soap solution.

Vomiting should be induced only if there is sufficient bulk (fluid) in the stomach to serve as a carrier for ingested poison.

Adequate dilution with water increases the efficacy of emetics.

Prevention of further toxin absorption

Contraindication of Emesis:

1- Unconscious & comatose patient because the vomitus may be aspirated into the lung & cause chemical pneumonitis.
2- If the patient has recently undergone surgery.
3- Ingestion of liquid hydrocarbons such as petroleum, gasoline, etc, these have low viscosity & surface area & can be readily aspirated into the lungs during emesis to cause chemical pneumonitis.
4- Children under 6 months because their gag reflex is poorly developed.
5- In case of corrosive agents ingestion to avoid further damage to the esophagus & oral mucosa.
6- patient with cardiovascular disease or emphysema or extremely weakened blood vessels to avoid risk of hemorrhage.

Prevention of further toxin absorption

A-Syrup of ipecac

Its action is slow, vomiting occurring after 30-60 min.; it considered to be toxic if large quantity was administered.
The active alkaloids are emetine & cephaline.
Ipecac cause emesis through both early & late phases of vomiting:
1- *Early vomiting occurs with in 30 min. & is due to direct stimulant action on the GIT.*
2- Second phase occurs after 30 min. resulting from direct stimulant action on the chemoreceptor triggerzone.

Advantages

Safe, well tolerated, & toxicity rare.
Disadvantages
Diarrhea & fever in addition to that emetine is considered as cardiotoxin.

Prevention of further toxin absorption

The recommended dose of syrup of ipecac

Age	Quantity
6-12 months	5-10 ml
1-12 years	15 ml
Adults	30 ml

The second dose may be given if the patient fails to vomit with in 20-30 min.

Prevention of further toxin absorption

B-Apomorphine

- Is a morphine derivative that produces rapid emesis usually within 3-5 min. through direct stimulation of the chemoreceptors triggerzone.
- It is give by IM only & may cause CNS & respiratory depression to the patient, so if shortness of breath occurs, antidote Naloxone should be given immediately.

Prevention of further toxin absorption

C-Soap solution

- When rapid emesis is indicated & syrup of ipecac is not available.
- It is a dish-washing liquid detergent.
- 2-3 tablespoonful should be mixed with 6-8 ounces of water (1 ounces=30 ml) , fluid ounce=2 tablespoon=0.0295 liter.

- Laundry detergents or dishwasher granular products should not be used because they are corrosive and may cause injury.

Prevention of further toxin absorption

3-Lavage

- It is a process of washing out the stomach with solution including water, saline, sodium bicarbonate, calcium salt, tannic, and potassium permanganate.
- The patients head should be slightly lower than the rest of the body to remove the stomach content effectively.
- Aliquots of 50-100 ml in adults should be instilled, allowed to mix, and then drained into a collection bag positioned below the patient. A minimum of 2 L are required to washed out most of the stomach contents.
- It is indicated when poisons must be quickly removed from the stomach or when emesis is contraindicated.
- Saline is recommended in children to prevent electrolyte imbalance.

Prevention of further toxin absorption

3-Lavage

- Lavage is not the first choice and it may be associated with many risks for e.g. the tube may be accidentally inserted into the trachea, so the patient's airway should be protected by intubation.
- Improperly used lavage can create a great risk of pulmonary aspiration, esophageal perforation or accelerated gastric emptying time to the intestine.
- If cool lavage solution is used too rapidly the body's core temperature may be dangerously lowered.
- Gastric lavage is contraindicated for the ingestion of most hydrocarbons, acid, alkali, and sharp objects.

Prevention of further toxin absorption

4-Adsorbents

- Are substances used to reduce absorption of an ingested poison e.g. kaolin, pectin, cholestyramine and activated charcoal.
- Activated charcoal may be mixed with tannic acid and magnesium oxide to form what is called " traditional universal antidote"
- Charcoal-complex passes through the intestinal tract and reduces the chance of chemical absorption.
- Effectiveness of adsorption is dependent on the quality of activated charcoal administration.
- Various flavoring and thickening agents have been added to increase the palatability of activated charcoal e.g. sodium alginate, carboxymethyl cellulose, gelatin and ice cream.

Prevention of further toxin absorption

4-Adsorbents

- Charcoal is pharmacologically inactive, not absorbed systemically and large dose cause constipation.
- The usual recommended dose:
  50-100 gm for adult
  25-50 gm for child
  1 gm/kg for infant
- For maximal effectiveness, activated charcoal should be administered within 30 min of poison ingestion.
- For anticholinergic & sedative drugs, because of their slowing gastric emptying effect, beneficial effects have been obtained when activated charcoal was given 6-8 hrs after poison ingested.
- In case of aspirin poison, 9-16 hrs interval between ingestion of drug & charcoal has stilled produced beneficial results.

Prevention of further toxin absorption

4-Adsorbents

Side effects of charcoal

1- gritty sensation (small pieces of sand or very small stones) in the mouth

2- temporarily discoloration to the gum and mouth

3- stick to the throat so it is not palatable for children.

Activated charcoal should not be given within 30 min. of syrup of ipecac, if both are administered, ipecac will decrease charcoal amount by vomiting and charcoal adsorbs emetin and cephaline which are the active emetic which are the active emetic alkaloids of ipecac that may lead to abolish their pharmacologic action.

Prevention of further toxin absorption

- In case of paracetamol toxicity activated charcoal has been shown to bind acetaminophen effectively, it is not recommended for concurrent use when N-acetyle cysteine is indicated as the antidote for acute acetaminophen poisoning, but recent studies reported that both can be used.

Prevention of further toxin absorption

5-Cathartics

- Saline cathartics are desired to remove toxic substances from GIT
- As the contact site between the poison and absorption sites is reduced, the potential for toxicity will be decreased, so the evacuation action of saline cathartics will decrease the drugs absorption that may lead inturn to decrease systemic poisoning.
- Castor oil can be used for phenol intoxication and mineral oil for fat soluble vitamins over doses.
- The use of sorbitol at doses of 1-1.5 gm/kg as cathartic has been preferred over other osmotically acting drugs like magnesium and sodium sulfate. It is associated with fewest electrolyte abnormality.

Prevention of further toxin absorption

5-Cathartics

Cathartics should not be used in the following conditions:

1-The poison is strongly corrosive.

2-Bowel sounds are absent.

3-The patient has electrolyte disturbances.

4-Sodium containing cathartics should be avoided by persons with CHF or other conditions where fluid retention is significantly dangerous.

- The use of concentrated disodium phosphate enema has led to hypernatremia, hyperphosphatemia and hypercalcemia.

5-Magnesium containing cathartics should not be given to persons with compromised renal function because the possibility of causing CNS depression due to accumulation of high conc. of Mg in serum.

Prevention of further toxin absorption

6-Whole bowel irrigation

- The procedure is also used to cleanse the entire GIT before surgery
- The solution most commonly used is a sodium sulfate and polyethylene glycol electrolyte solution that is not absorbed and does not lead to fluid or electrolyte imbalance.
- This method decreases absorption of salicylate, lithium, and ampicillin.
- Whole bowel irrigation has also been used in overdoses of iron and zinc sulfate and in removing ingestion of cocaine. It is safe in children.

Prevention of further toxin absorption

7-Demulcent

- Many plants and chemicals cause oral and gastric mucosal irritation but no serious toxicity.
- Management of these acute ingestions may include ice cream, milk or another soothing demulcent to reduce irritation.
- Egg white serve as a source of readily available protein have been given for corrosive intoxications.
- Demulcent serves as important placebo or palliative therapy.

Topical decontamination

- Many lipid soluble chemicals can be absorbed through the skin and causes systemic toxicity within min.
- After dermal exposures, all contaminated clothing should be removed.
- Skin should flushed with water washed with mild soap.
- No cream, ointments or bandages should be placed over the contaminated area.
- Many substances are absorbed within min. through the cornea, causing permanent damage, including loss of eyesight.
- When ocular contamination occurs, irrigation with warm water must be immediately introduced and continued for at least 15-20 min., contact lenses should be removed and the eyes held directly under a softly flowing stream of water.
- Medicine dropper, irrigation syringe are inadequate for rinsing the eyes because they do not hold a sufficient reservoir of water.

5-Methods to increase elimination of toxic agents

1-Forced diuresis and PH alteration

- Used to removed chemicals and drugs from blood.
- It is useful when compounds or active metabolites are eliminated by the kidney and diuresis enhances their excretion.
- The used diuretic agents are manitol (which is osmotic diuretic) and furosemide (loop diuretic).
- Nonionized (nonpolar) compounds move easily across cell memb., where as ionized (polar) compounds are much less diffusible, so the goal of urinary PH manipulation is to enhance renal excretion of a compounds by increasing the amount of ionized (polar) form in the kidney so decrease its tubular absorption.
- Ideally increase elimination of weak acid will occur when urinary PH is more alkaline, while enhanced elimination of weak base will occur when urinary PH is more acidic.

Methods to increase elimination of toxic agents

1-Forced diuresis and PH alteration

- Alkaline diuresis is achieved by administration of sodium bicarbonate 1-2 mEq/kg every 3-4 hrs.
- The objective is to increase urinary PH between 7 & 8.
- The potential uses of urine alkalization have been with weak acid such as salicylate, and phenobarbital.
- Acid diuresis is possibly by using ammonium chloride, 75 mg/kg/24 hr
- The end point of acidification is a urinary PH between 5.5 & 6.
- Acid diuresis used to increase elimination of weak bases such as amphetamine, phencyclidine & quinidine.

Methods to increase elimination of toxic agents

2-Dialysis and hemoperfusion

- Dialysis depends on the principle of diffusion.
- A diffusible chemical dissolved in water partitions across a semipermeable membrane and the solution moves from an area of high conc. i.e. the blood to one of lower conc. i.e. the dialyzing solution.
- Dialysis & perfusion methods should never replace the use of more specific treatment or antidote.

Methods to increase elimination of toxic agents

3-Peritoneal dialysis

- It is the least effective method of removing most poisons.
- The procedure is undertaken by inserting a tube through a small incision made in the midabdominal area into the peritoneum.
- The peritoneal memb. serves as the semipermeable (dialyzing) memb.
- In this way the dialyzable chemical diffuses from blood across the peritoneal memb. into the dialyzing fluid (move from area of higher conc. to lower conc.)
- Complication of peritoneal dialysis include:

A. Abdominal pain
B. Intraperitoneal bleeding
C. Intestinal, bladder, liver, or spleen perforation
D. Water & electrolyte imbalance & protein loss

Methods to increase elimination of toxic agents

4-Hemodialysis

- The same basic principle applies to hemodialysis (extracorporeal dialysis); for peritoneal dialysis an in vivo peritoneal memb. is utilized; in hemodialysis a cellophane bag (artificial kidney forms the semipermeable mem.)
- Two catheters are inserted into the patients femoral vein, blood is pumped from one catheter through the dialysis unit across the semipermeable memb. and back through the other catheter.
- The solubilized chemical diffuses through the semipermeable memb. into the dialysis solution.
- The chemical to be removed by dialysis must have low molecular weight & small molecular size to diffuse passively across the dialyzing memb.

Methods to increase elimination of toxic agents

4-Hemodialysis

- Protein are too large to pass through the memb. so hemodialysis is less effective for chemicals or drugs that are highly protein bound.
- Complication include:
    1. *Clotting & leakage of blood from around connection*
    2. *Hypotension*
    3. *Convulsion*
    4. *Arrhythmias*
    5. *Infection & hematological defects*

Methods to increase elimination of toxic agents

5-Hemoperfusion

- It is more effective than peritoneal dialysis & hemodialysis for removing intoxication compounds particularly those that are lipid soluble or protein bound.
- Blood is withdrawn via an arteriovenous or venovenous shunt and passed directly over the adsorbing materials (example activated charcoal) contained in sterile column.

Methods to increase elimination of toxic agents

- Indication for hemoperfusion in sever intoxication are evaluated by two criteria:

1-Whether the adsorbent will eliminate the chemical from the blood.

2-The volume of distribution must be small and half life of the intoxicant relatively long so the drug continue to be drawn from the tissue to the blood & consequently removed.
Complications: trapping of white blood cells & platelets.

6-Specific Antidotes

Specific antidotes can be classification into:

1-Chemical

2-Receptor

3-Dispositional

4-Functional

1-Chemical antidote

React with the poisonous chemical to produce a compound of lesser toxicity or one that is absorbed to lesser degree than the parent compound.

Example: in oxalic acid toxicity absorption produces renal damage. Calcium salts react with oxalic acid to yield a poorly soluble compound, calcium oxalate which passes through the intestine without being absorbed.

Specific Antidotes

2-Receptor antidote

Compete with the poison for receptor sites.

Example include:

- Naloxone reversal of morphine induced respiratory depression.
- Cholinergic blockade by atropine, where the specific antidote is physostigmine (a reversible cholinesterase inhibitor) that lead to increase acetylcholine level because it compete with atropine at receptor site.

Specific Antidotes

3-Dispositional antagonism

Involve alteration of absorption, metabolism, distribution or excretion of toxic agents to reduce the amount available to tissues.

Example: acetaminophen overdose a toxic metabolite causes hepatotoxicity, conversion of this toxic to a nontoxic form occurs by conjugation with glutathione, a sulfhydryl (-sh) group donor.

N-acetylcystein is also a source of (-sh) groups which serve the same function as endogenous GSH.

Specific Antidotes

4-Functional (physiologic) antagonist

Act on one biochemical system to produce effects that are opposite from those produced on another system

Example: during anaphylactic reaction after administration of a drug, the individual experiences sever breathing difficulties due to in part to intense bronchoconstiction.

Epinephrine reverses this effect and breathing is return normal.

Examples on Antidotes:

Poison substance	Antidote
Acetominophen	(N-acetylcysteine)
Anticholinergics	Physostigmine
warfarin	VitaminK1
heparin	protamine
Benzodiazepines	Flumazenil
Botulism	Botulinum Antitoxin
Beta Blockers	Glucagon
Calcium Channel Blockers	Calcium
Cholinergics	Atropine
Organophosphate Overdose	Pralodixime
Cyanide	Amyl Nitrate, Hydroxycobalamin
Digoxin	Digoxin Fab Antibodies
Iron	Deferoxamine
Isoniazid	Pyridoxine
Lead	BAL (Dimercaprol), EDTA, DMSA
Opiods	Naloxone

Supportive care & clinical follow-up

- The supportive care phase of poison treatment is very important.
- Close clinical monitoring can detect these later phase poisoning complications & allow for prompt medical intervention.
- Another important component of the supportive care phase of poison treatment is the psychiatric assessment.
- In many cases, it is not possible to perform a psychiatric interview of the patient during the early phases of the treatment & evaluation.
- Once the patient has been stabilized & is able to communicate, a psychiatric evaluation should be obtained.


Thank you!