IN THE NAME OF GOD

TOXICITY & KIDNEY INVOLVEMENT

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Introduction

An overdose is a medical emergency that requires immediate medical attention

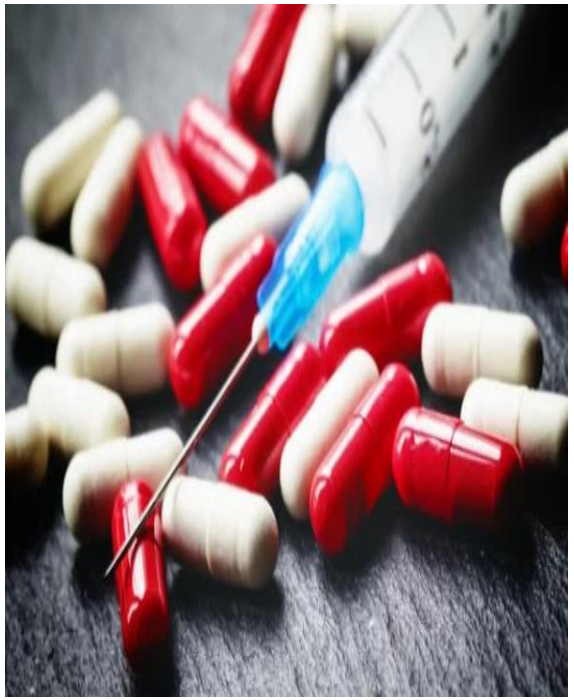
- Substances toxic to the kidney are legion in the modern world.
- Acute kidney injury (AKI) induced by poisonous or primarily nephrotoxic substances, may be community acquired with ingestion or inhalation or nosocomial.
- Many nephrotoxic plants, medications, chemicals and illicit drugs can induce AKI by varying pathophysiological pathways.
- Moreover, the epidemiology of toxic AKI varies depending on country, regions within countries, socioeconomic status and health care facilities.

Ren Fail. 2019; 41(1): [illegible]6–594.

EPIDEMIOLOGY

In 2017, the American Association of Poison Control Centers reported more than 2.1 million human toxic exposures across the United States.

Most reported exposures were due to a few classes of prescription medications (analgesics, sedative/hypnotics, antipsychotics, antidepressants) or readily available cleaning or personal care products.



Accidental exposures are the most common among children, while suicidal ingestions are predominant among adults

In current times, according to one retrospective, case-control study using the data NPDS, of the approximate 16.8 million exposures , has reported .
There were 16 444 single substance exposures with renal effects, of which 9074 cases had serious kidney complications (55.2%).
Poisoned patients with renal impairment had higher rates of renal replacement therapy initiation (27.7%) and death (10.9%)

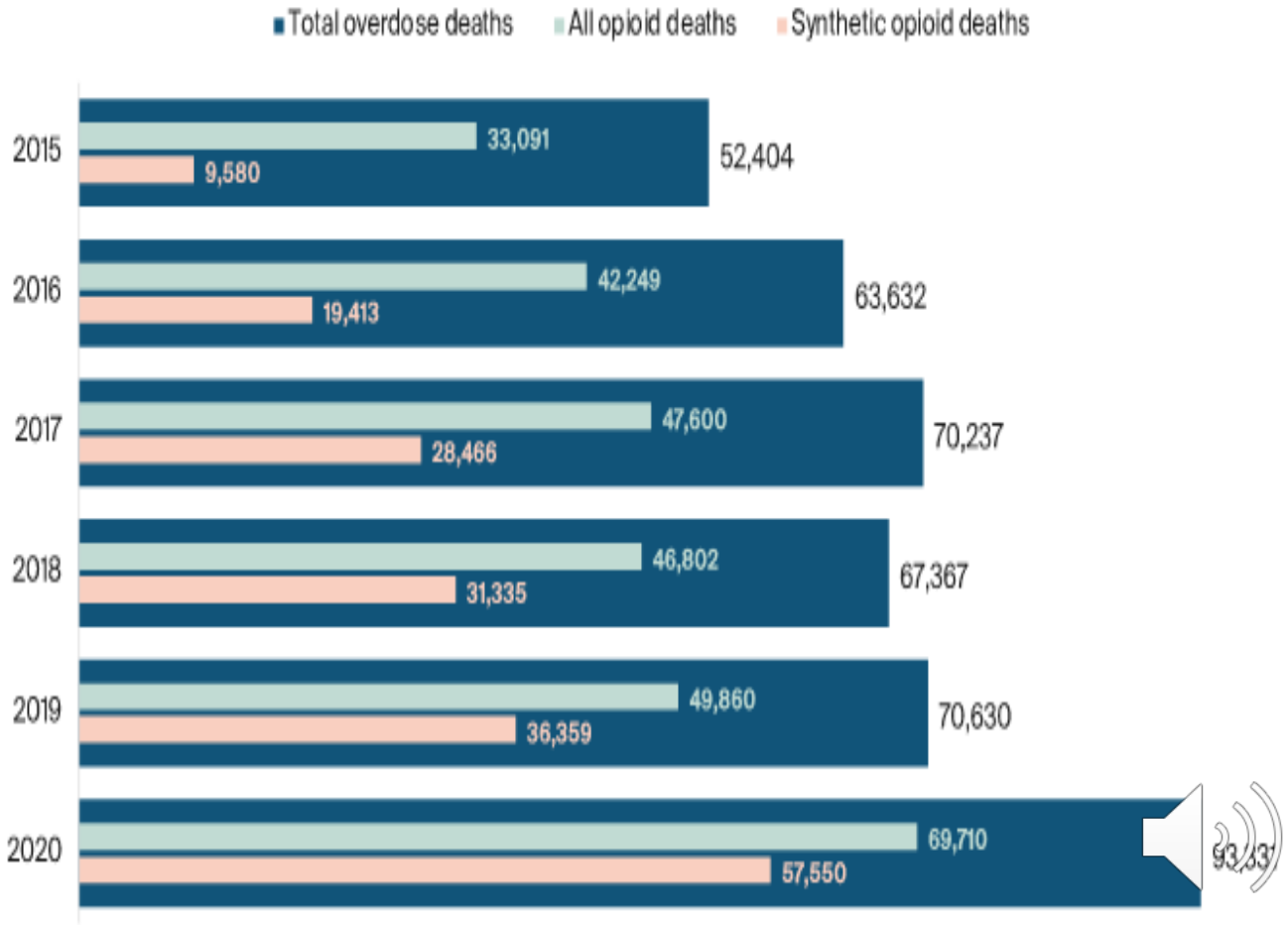
Ren Fail. 2019; 41(1): 576–594

EPIDEMIOLOGY

- **Synthetic Opioids Including Fentanyl Helped Drive Record-High Overdose Deaths in 2020**
- The CDC data show that drug overdose deaths reached a record high of 93,331 in 2020.
- Since 2015 the percentage of all U.S. deaths attributed to overdoses has grown from 1.9 percent to 2.8 percent, even as COVID-19 increased total deaths by more than 300,000 in 2020.
- The number of Americans dying from opioid overdose remain high
- overdose deaths rose dramatically for nearly every racial/ethnic group and age range.
- Men, younger people, and Black, Latinx/Hispanic, American Indian/Alaska Native, and Asian American communities reported the highest proportional increases compared to 2019.

Overdose deaths exploded to more than 90,000 in 2020, and synthetic opioids were involved in more than 60 percent of all overdose deaths.

Annual drug overdose deaths



There are four types of poisoning:

1. Fulminant - Produced by a massive dose. Death occurs very rapidly, sometimes without preceding symptoms, the patient appearing to collapse suddenly.

2. Acute - Produced by a single dose or several small doses taken in a short period. Onset of symptoms is abrupt.

3. Chronic - Produced by small doses taken over a long period. Onset is insidious.

4. Subacute - Characterized by a mixture of features of acute and chronic poisoning.

Causes

Acute alcohol intoxication

- Ethyl alcohol
- Methanol poisoning
- Ethylene glycol poisoning

•Opioid overdose

•Sedative-hypnotics

•Barbiturate overdose
•Benzodiazepine overdose

•Uncategorized sedative-hypnotics

•Ethchlorvynol (Placidyl)

- GHB
- Glutetimide (Doriden)
- Ketamine

• stimulants

- Cocaine overdose
- Amphetamine overdose
- Methamphetamine overdose

• tobacco

- Nicotine poisoning

• poly drug use

- Drug "cocktails" (speedballs)

•Medications

- Aspirin poisoning
- Paracetamol poisoning
- Paracetamol toxicity
- Tricyclic antidepressant overdose
- Vitamin poisoning

•Pesticide poisoning

- Organophosphate poisoning
- DDT

•Inhalants

•Lithium toxicity

Clinical manifestations

The majority of poisoned patients presenting to the casualty (emergency) department are victims of acute exposure. In most cases, the poisoned patient presents with one or more of the following non-specific features:

1. Impairment of consciousness
2. Respiratory/Cardiovascular depression
3. Dehydration due to vomiting/diarrhoea
4. Hypothermia
5. Convulsions
6. Cardiac arrhythmias

Toxic Syndromes: Toxic syndrome or toxidrome is a constellation of toxic effects comprising a set of clinical fingerprints for a group of toxic chemicals.

Type of toxic syndrom

1. Anticholinergic syndrome

Causes: Antihistamines, anti-parkinsonian drugs, atropine, scopolamine, amantadine, antipsychotic drugs, antidepressants, antispasmodics, skeletal muscle relaxants, many plants (especially Datura), and fungi (e.g. Amanita muscaria).

Symptomatology: Delirium with mumbling speech, tachycardia, dry hot skin, mydriasis, myoclonus, urinary retention, decreased bowel sounds. Convulsions and arrhythmias in severe cases.

2. Cholinergic syndrome

Causes: Organophosphates, carbamates, parasympathomimetic drugs, and some mushrooms

Symptomatology: Confusion, CNS depression, salivation, lacrimation, urinary and faecal incontinence, vomiting, sweating, fasciculations, seizures, miosis, pulmonary oedema, tachy/bradycardia

3. Sympathomimetic syndrome

Causes: Cocaine, amphetamines, upper respiratory decongestants (phenylpropanolamine, ephedrine, and pseudoephedrine)

Symptomatology: Paranoia, delusions, tachycardia, hypertension, hyperpyrexia, sweating, mydriasis, seizures, arrhythmias

4. Sedative syndrome

Causes: Opiates, barbiturates, benzodiazepines, ethanol, methaqualone, meprobamate, ethchlorvynol, glutethimide, clonidine

Symptomatology: Miosis, hypotension, bradycardia, hypothermia, CNS depression, hyporeflexia, coma, rarely convulsions.

Common toxidromes

Toxidromes	*Mental status*	*Pupils*	*Vitals*	*Other manifestations*	*Examples of tox agents*
Sympathomimetic	Hyper alert, agitation, hallucination, paranoia	Mydriasis	Hyperthermia, tachycardia, hypertension, widened pulse pressure	Diaphoresis, tremors, hyperreflexia, seizures	Cocaine, amphetamines, ephedrine, theophylline, caffeine
Anticholinergic	Agitation, hallucinations, delirium, coma	Mydriasis	Hyperthermia, tachycardia, hypertension, tachypnea	Dry flush skin, dry mucous membranes, decreased bowel sounds, urinary retention, myoclonus	Antihistamines, TCA, antiparkinsonism agents, atropine, antispasmodics
Hallucinogenic	Hallucinations, perceptual distortions, depersonalization, agitation	Mydriasis (usually)	Hyperthermia, tachycardia, hypertension, tachypnea	Nystagmus	Phencyclidine, MDMA, MDEA
Opioid	CNS depression, coma	Miosis	Bradypnea, apnea	Hyporeflexia, pulmonary edema, needle marks	Heroin, morphin methadone, diphenoxylate
Sedative-hypnotic	CNS depression, confusion, stupor,	Variable	Often normal; hypothermia,	Hyporeflexia	Benzodiazepine barbiturates,

Diagnostic Evaluation

- CBC –Electrolytes-ABG
- LFTs ; BUN,CR; CXR
- ECG
- Serum lactate
- CPK LDH
- AXR
- Serum Toxin
- ASA level
- Tylenol level
- Serum OSM
- Urine Toxin opiates, benzodiazepines, cocaine metabolites, barbiturates, tricyclic antidepressants, tetrahydrocannabinol, phencyclidine

- urinary microRNAs can be used as early renal biomarkers following nephrotoxic-AKI (snakebite envenoming, oxalic acid, paraquat, and glyphosate poisoning)

Scientific Reports **volume 11**, Article number: 9165 (2021)

Immunoassay screening tests:

These assays are inexpensive and provide rapid results, usually within one hour.

Positive and negative screens for drugs do not absolutely confirm or refute poisoning diagnoses and require further evaluation.
some drugs that present in therapeutic amounts, such as opioids and benzodiazepines, may be detected by the screen even though they are causing no contributing clinical symptoms.

Qualitative toxic screening of urine, blood, or other body fluids (commonly by liquid and gas chromatography and mass spectrometry) is expensive can be perform , in patients with severe or unexplained toxicity

The Individualized Management Approach for Acute Poisoning",, vol. 2021

IN METABOLIC ACIDOSIS

Anion Gap = Na^+ - $[Cl^- + HCO_3^-]$= 8 to 12 mEq/L

- Toxins with increased AG:
  - Methanol
  - Paraldehyde
  - INH
  - Fe
  - Ethylene glycol
  - Salicylates
  - CO
  - Cyanide

  Hydrogen Sulfide
  ETOH (ketones)
  Metformin
  Phenformin
  Sulfur
  Theophylline
  Toluene

Toxins with decreased AG:

Lithium
Bromide

Osmolar Gap (OG)

Serum OSM: 2[Na] + [Glc]/18 + [BUN]/2.6

OG: Measured OSM-Calculated OSM

Normal OG: -3 to 10 mOSM/kg H2O

Toxins with increased OG

Methanol
Ethanol
Ethylene glycol
Acetone
Isopropanol

- An increase in the osmolar gap indicates the presence of a low molecular weight, osmotically active substance in the serum

Normal osmolar gap does not rule out toxic alcohol intoxication because;

(1) the patient's baseline osmolar gap is not known;

(2) as metabolism of the parent toxic alcohol compound ensues , the osmolar gap narrows with a concomitant increase in the anion gap);

(3) the contribution of any osmolaritically active compound to the osmolar gap related to the compound's molecular weight.

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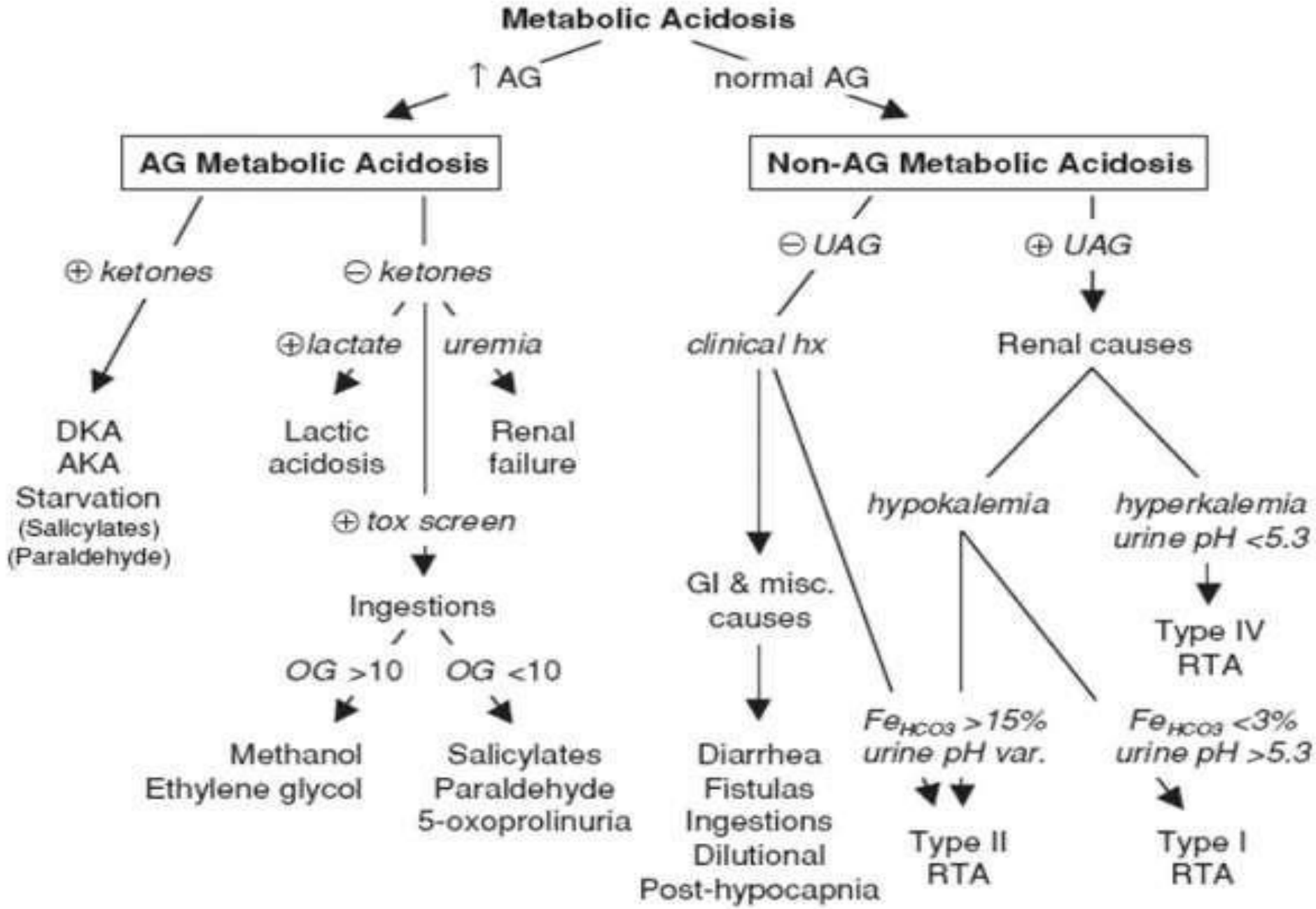

Metabolic Acidosis
↑ AG
normal AG
AG Metabolic Acidosis
Non-AG Metabolic Acidosis
⊕ ketones
⊖ ketones
⊖ UAG
⊕ UAG
⊕ lactate
uremia
clinical hx
Renal causes
DKA
AKA
Starvation
(Salicylates)
(Paraldehyde)
Lactic acidosis
Renal failure
hypokalemia
hyperkalemia
urine pH <5.3
⊕ tox screen
Ingestions
GI & misc. causes
Type IV RTA
OG >10
OG <10
FeHCO3 >15%
urine pH var.
FeHCO3 <3%
urine pH >5.3
Methanol
Ethylene glycol
Salicylates
Paraldehyde
5-oxoprolinuria
Diarrhea
Fistulas
Ingestions
Dilutional
Post-hypocapnia
Type II RTA
Type I RTA

Elimination Enhancement

Increased rate of removal of an agent to reduce mortality, complications, more invasive interventions, or LOS. In practice useful only when positive risk-benefit analysis and:

- Severe toxicity
- Poor outcome despite supportive care/antidote
- Slow endogenous rate of elimination
- Suitable pharmokinetic properties

The various methods of eliminating absorbed poisons from the body include the following:

1. Forced Diuresis
2. Extracorporeal techniques
   - Haemodialysis
   - Haemoperfusion
   - Peritoneal dialysis
   - Haemofiltration
   - Plasmapheresis
   - Plasma perfusion
   - Cardiopulmonary bypass.

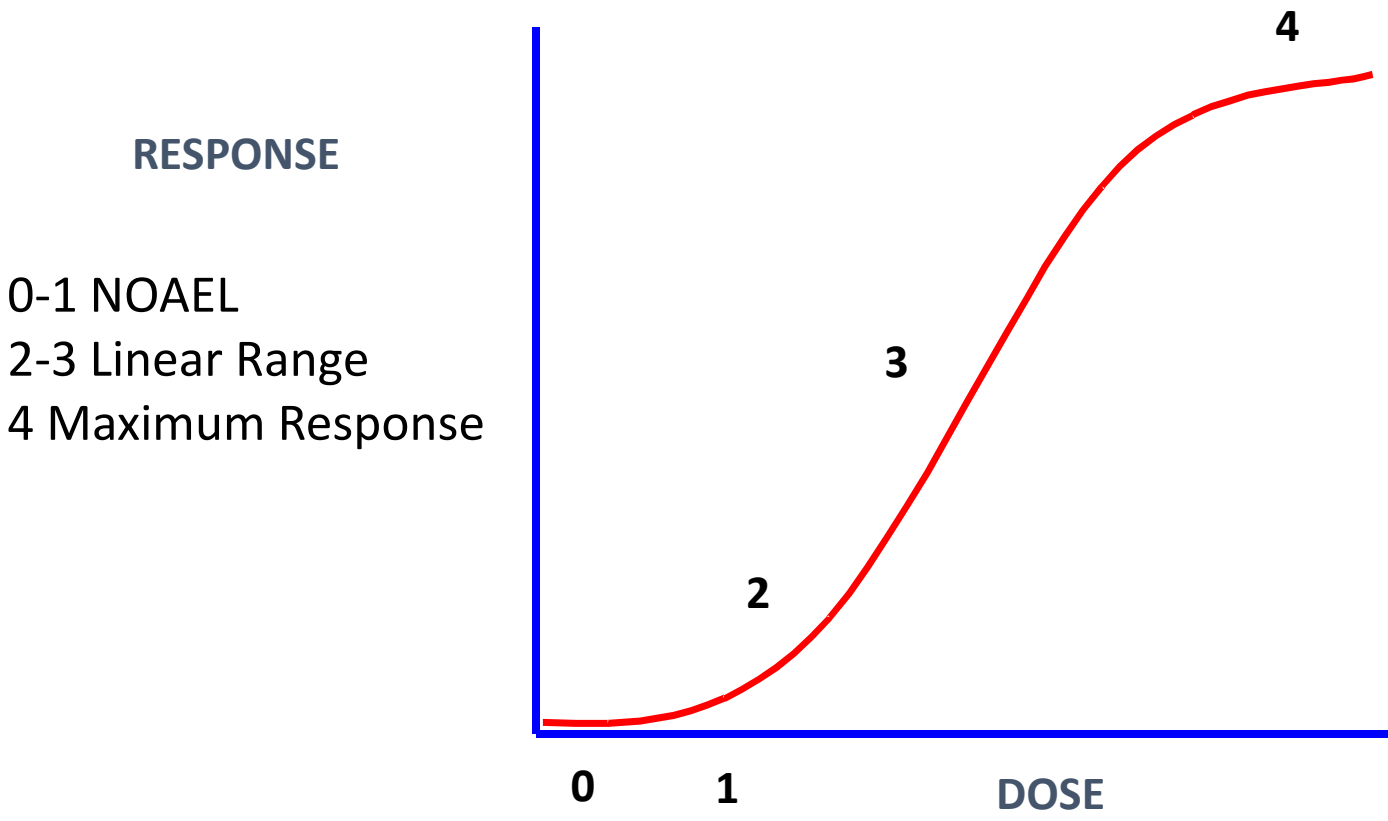
TOXICOKINETICS & TOXICODYNAMICS

The term **toxicokinetics** denotes the absorption, distribution, excretion, and metabolism of toxins, toxic doses of therapeutic agents, and their metabolites.

The term **toxicodynamics** is used to denote the injurious effects of these substances on body functions.

Dose-Response Relationship:

As the dose of a toxicant increases, so does the response.



DOSE DETERMINES THE BIOLOGICAL RESPONSE

The therapeutic index and the overlap of therapeutic and toxic response curves must be considered.

In the case of a drug with a linear dose-response curve (drug A), lethal effects may occur at 10 times the normal therapeutic dose.

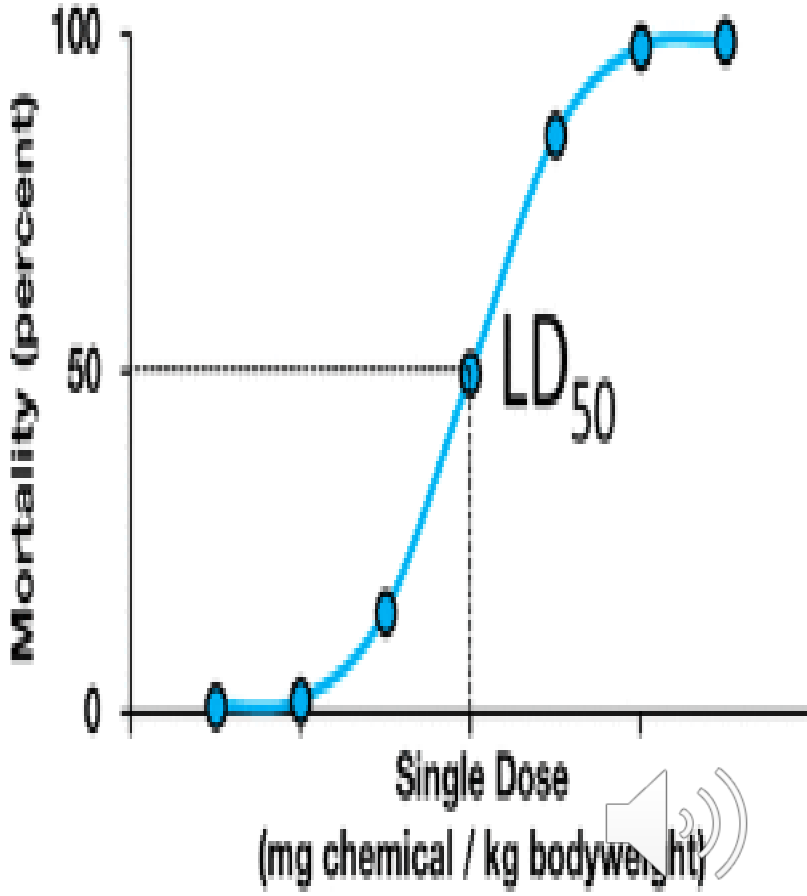
In contrast, a drug with a curve that reaches a plateau (drug B) may not be lethal at 100 times the normal dose

LD_{50}

The acute lethality hazard is typically determined using the LD_{50} which is defined as the median dose predicted to kill 50% of a given test population.

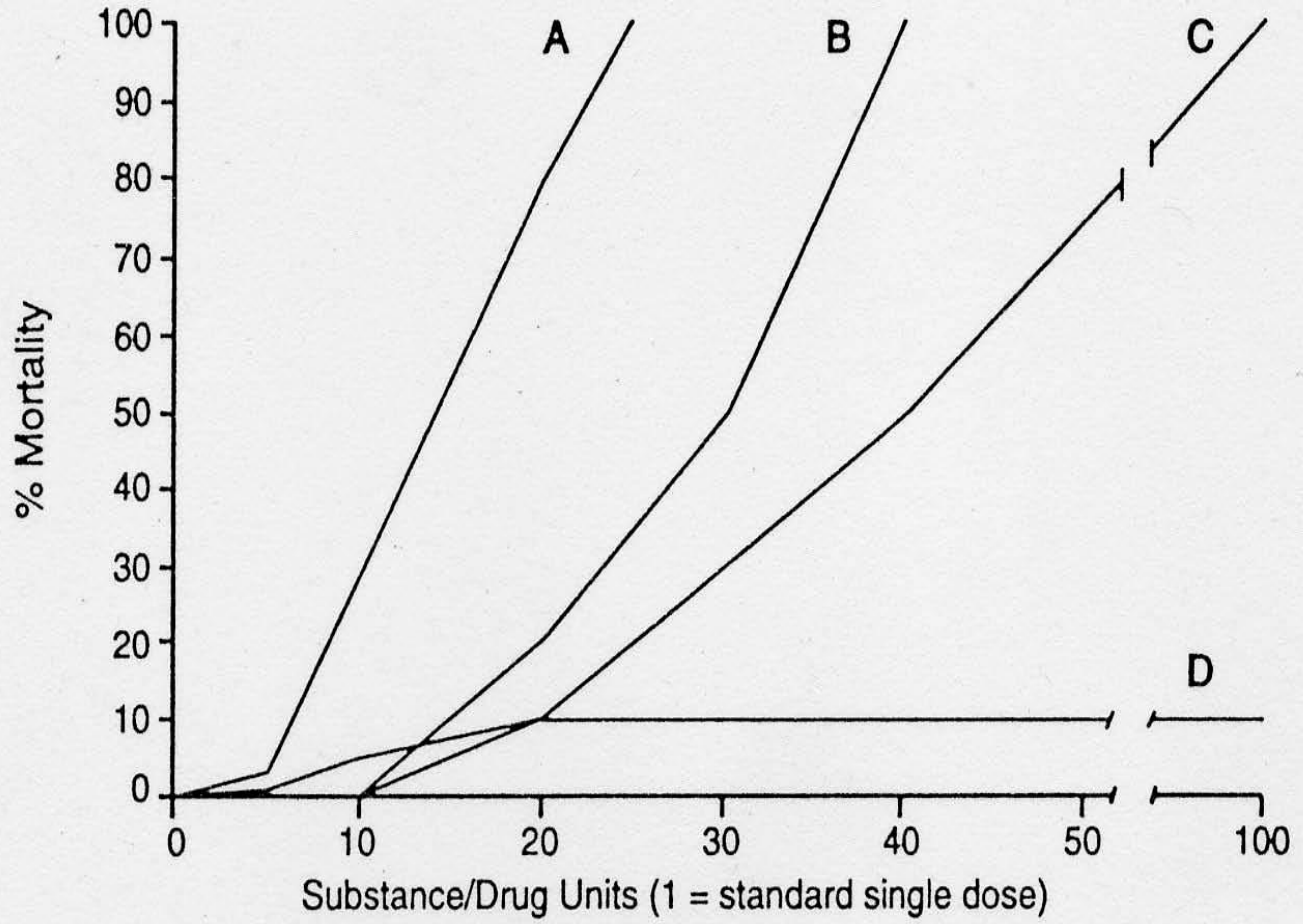
Anything with an acute oral LD50 over 5 g/kg bw (or 5000 mg/kg bw) is considered to be practically nontoxic, per the Hodge-Sterner scale:

No.	Term	LD_{50} (Rat, Oral)
1	Extremely Toxic	Less than 1 mg kg^{-1}
2	Highly Toxic	1 - 50 mg kg^{-1}
3	Moderately Toxic	50 - 500 mg kg^{-1}
4	Slightly Toxic	500 - 5000 mg kg^{-1}
5	Practically Non Toxic	5000 - 15,000 mg kg^{-1}



Patterns of Mortality Risk From Drugs/Substance Overdose

A Theoretical Model



A - High toxicity: Digoxin, tricyclic antidepressant, theophylline, carbon monoxide, cyanide

B - Intermediate: Acetaminophen, salicylate, phenobarbital

C - Low: Propranolol (immediate-release)

D - Threshold for overdose effect: Atropine, phenylpropanolamine

LD_{50} Comparison

Chemical	LD_{50} (mg/kg)
Ethyl Alcohol	10,000
Sodium Chloride	4,000
Ferrous Sulfate	1,500
Morphine Sulfate	900
Strychnine Sulfate	150
Nicotine	1
Black Widow	0.55
Curare	0.50
Rattle Snake	0.24
Dioxin (TCDD)	0.001
Botulinum toxin	0.0001

FACTORS DETERMINING SEVERITY OF TOXICITY

- **Duration and concentration** of a substance at the portal of entry.
- **Rate and amount** of the substance that can be absorbed.
- **Distribution** in the body and **concentration** of the substance at specific body sites.
- **Efficiency** of biotransformation and nature of the metabolites.
- **Ability** of the substance or its metabolites **to pass through cell membranes** and come into contact with specific cell components (for example, DNA).
- **Amount and duration of storage** of the substance (or its metabolites) in body tissues.
- **Rate and sites of excretion** of the substance.
- **Age and health status** of the person exposed.

SPECIAL ASPECTS OF TOXICOKINETICS

ADME:

Absorption, Distribution, Metabolism, and Excretion

- **Absorption:** ability of a chemical to enter the blood
- Inhalation--readily absorb gases into the blood
- Ingestion--absorption through GI tract stomach small intestine
  - 1st Pass Effect (liver can modify)
  - Reduction in the first-pass effect can dramatically increase the absorption of oral drugs even with therapeutic doses like in patients with cirrhosis
- Drugs may injure the epithelial barrier of the gastrointestinal tract and thereby increase absorption.
- Dermal--absorption through epidermis

"The Individualized Management Approach for Acute Poisoning",, vol. 2021

Distribut*ion of drug* the process in which a chemical agent trans locates throughout the body;

blood flow

characteristics of toxicant (affinity for the tissue)

Water & lipid solubility

- Lipid soluble drugs are more penetrate rapidly into cell then water

The are directly proportional to higher lipid soluble drugs are greater rate if absorption form GIT

Ionization

- Unionized drugs are lipid soluble while ionized are water soluble
- Hence, unionized drugs are better absorbed then ionized drugs in cell membrane

Rout of administration

Parentrals routes are widely distributed the body & tissue then oral route

iv > inhale > ip > im > ingest > topical

Protein Binding

in the case of hypoalbuminemia for highly albumin-bound substances,increases the free fraction of the drug in the blood, which increases the risk of toxicity,

The drugs with low protein binding affinity are more likely to be dialyzed,

while drugs with high protein binding affinity are more likely to be removed by plasma exchange

Volume of Distribution

A large Vd, implies that the drug is not readily accessible to hemodialysis
The drugs with large volumes of distribution (> 5 L/kg) include antidepressants, antipsychotics, antimalarials, opioids, propranolol, and verapamil.

Drugs with a relatively small V (< 1 L/kg) include salicylate, ethanol, phenobarbital, lithium, valproic acid, and phenytoin

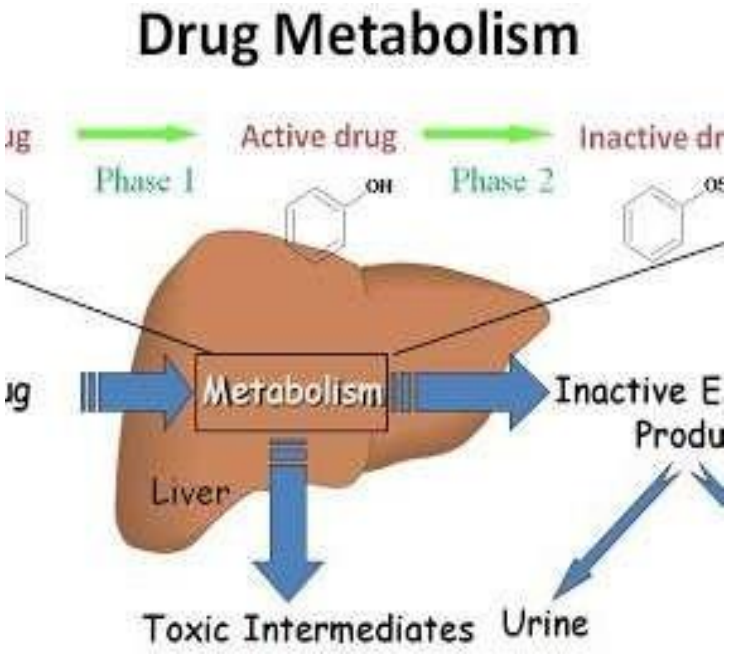
Poisonous substances undergoing redistribution or having a large volume of distribution may induce delayed toxicity manifestations

Clearance

Clearance is a measure of the volume of plasma that is cleared of drug per unit time
The total clearance for most drugs is the sum of clearances via excretion by the kidneys and metabolism by the liver that ,important to detoxification strategy

Overdosage of a drug can alter the usual pharmacokinetic
If the capacity of the liver to metabolize a drug is exceeded, the first-pass effect will be reduced and more drug will be delivered to the circulation.

- **Metabolism**
- **A chemical alteration of drug form living organism is called biotransformation**
- Key organs in biotransformation
  - LIVER (high)
  - Lung, Kidney, Intestine (medium)
  - Others (low)
- Biotransformation Pathways
  * Phase I--make the toxicant more water soluble
  * Phase II--Links with a soluble endogenous agent (conjugation)
  * If metabolites are active, as it will extend the duration of toxicity
  * Drug make to change first-pass effects (e.g., calcium channel blockers).



objective--make chemical agents more water soluble and easier to excrete
decrease lipid solubility --> decrease amount at target
increase ionization --> increase excretion rate --> decrease toxicity

Excretion

Two types of drug excretion

- Non- renal channel (bile, lungs ,intestine Skin ,saliva and milk)
- Renal Channel (mainly through kidney)
- Water soluble drugs mainly excreted in kidney that function are **impacted** affect of concentration.

Check first if the poison is eliminated mainly by the kidney in urine or not.
If so, the half-life will be affected.
This will affect the decisions to utilize enhanced elimination methods, including dialysis or urine alkalinization for weak acid drugs and the observation/disposition time

- The Individualized Management Approach for Acute Poisoning",, vol. 2021

EXTRACORPOREAL ELIMINATION

The toxins need to have a number of criteria to be effectively removed by extracorporeal elimination

low volume of distribution (<1.0 L/kg),
low molecular weight (<5000Da), relatively
low protein binding
low endogenous clearance.

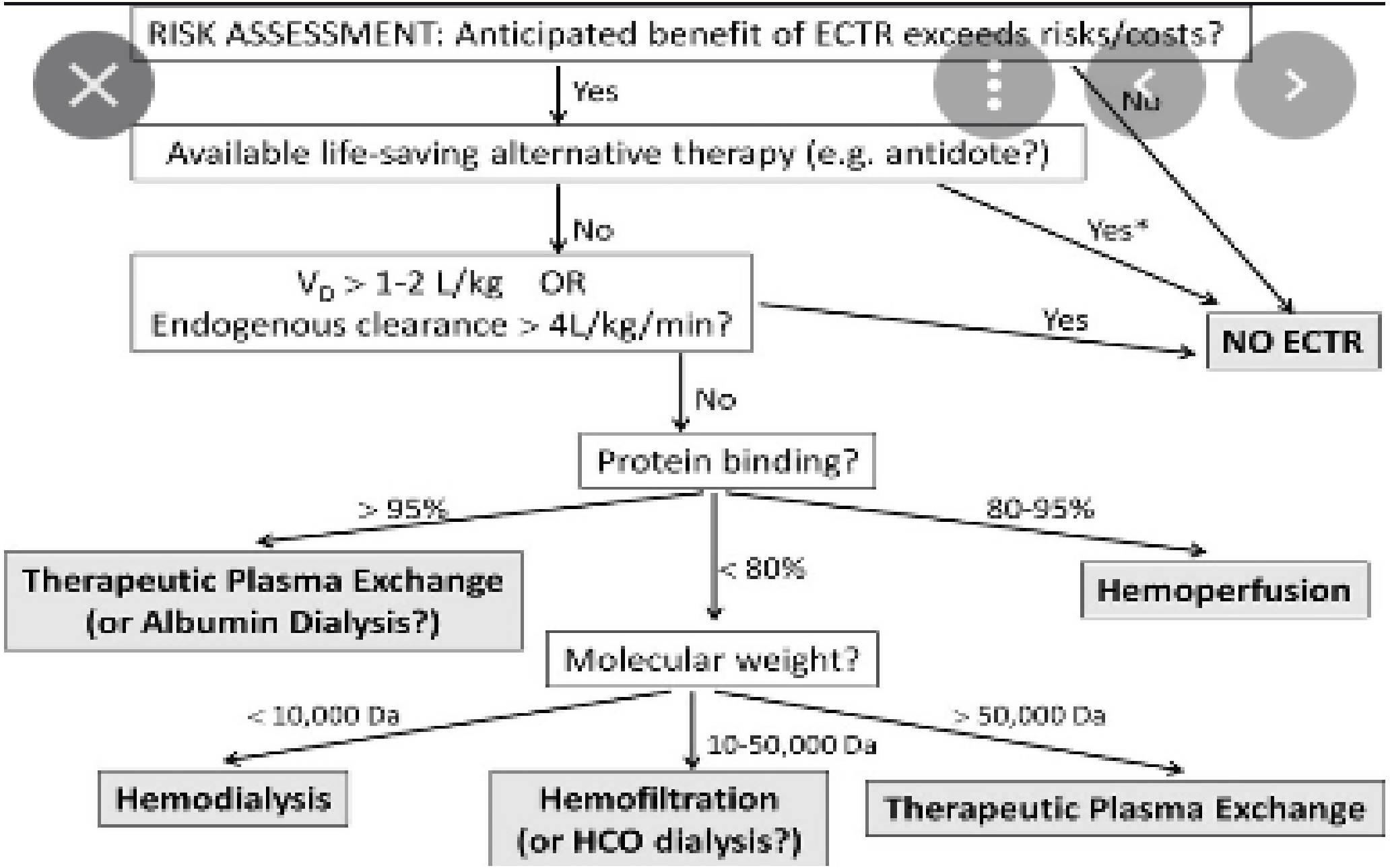
Box 12. Toxins accessible to hemodialysis (UNSTABLE)

Uremia
No response to conventional therapy
Salicylates
Theophylline
Alcohols (isopropanol, methanol)
Boric acid, barbiturates
Lithium
Ethylene glycol

Box 13. Enhanced elimination by charcoal hemoperfusion

Theophylline
Barbiturates
Carbamazepine
Paraquat
Glutethimide

General Approach to Poisoned Patient
: January 24th 2019


RISK ASSESSMENT: Anticipated benefit of ECTR exceeds risks/costs?
Yes
No
Available life-saving alternative therapy (e.g. antidote?)
Yes*
No
V_D > 1-2 L/kg OR
Endogenous clearance > 4L/kg/min?
Yes
NO ECTR
No
Protein binding?
> 95%
80-95%
< 80%
Therapeutic Plasma Exchange
(or Albumin Dialysis?)
Hemoperfusion
Molecular weight?
< 10,000 Da
10-50,000 Da
> 50,000 Da
Hemodialysis
Hemofiltration
(or HCO dialysis?)
Therapeutic Plasma Exchange

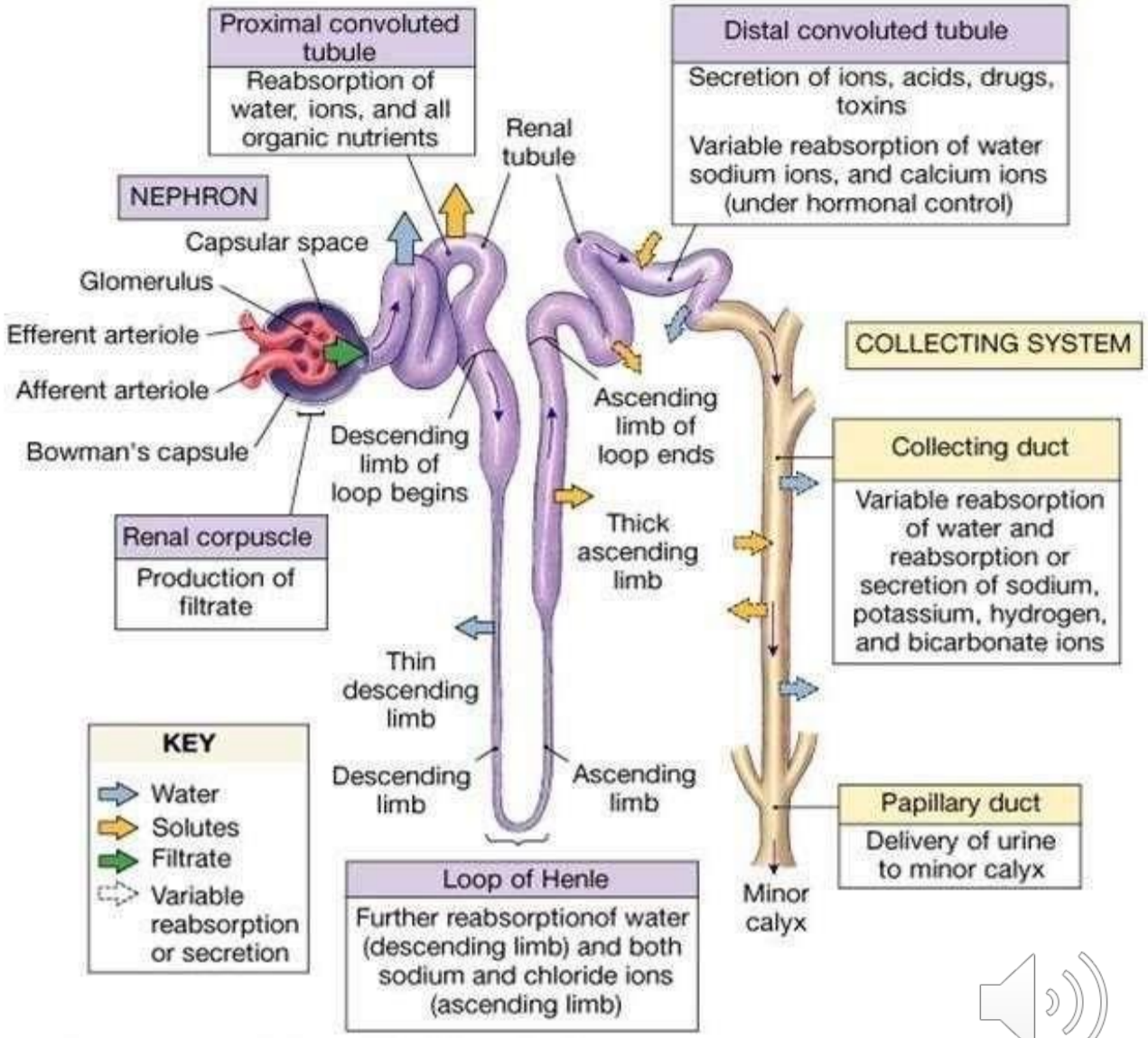
Substance abuse and the kidney

Metabolism and excretion of exogenously administered therapeutic agents as well as environmental exposures are other major functions of kidney.

The renal complications of drug abuse are spectrum of glomerular, interstitial and vascular diseases

.

some substances are directly nephrotoxic, These effects are often chronic and irreversible, but occasionally acute with possible recovery.



QJM: An International Journal of Medicine, Volume 93, Issue 3, March 2000, Pages 147–152

Ren Fail. 2019; 41(1): 576–594

Environmental (Agro)chemical nephrotoxicity

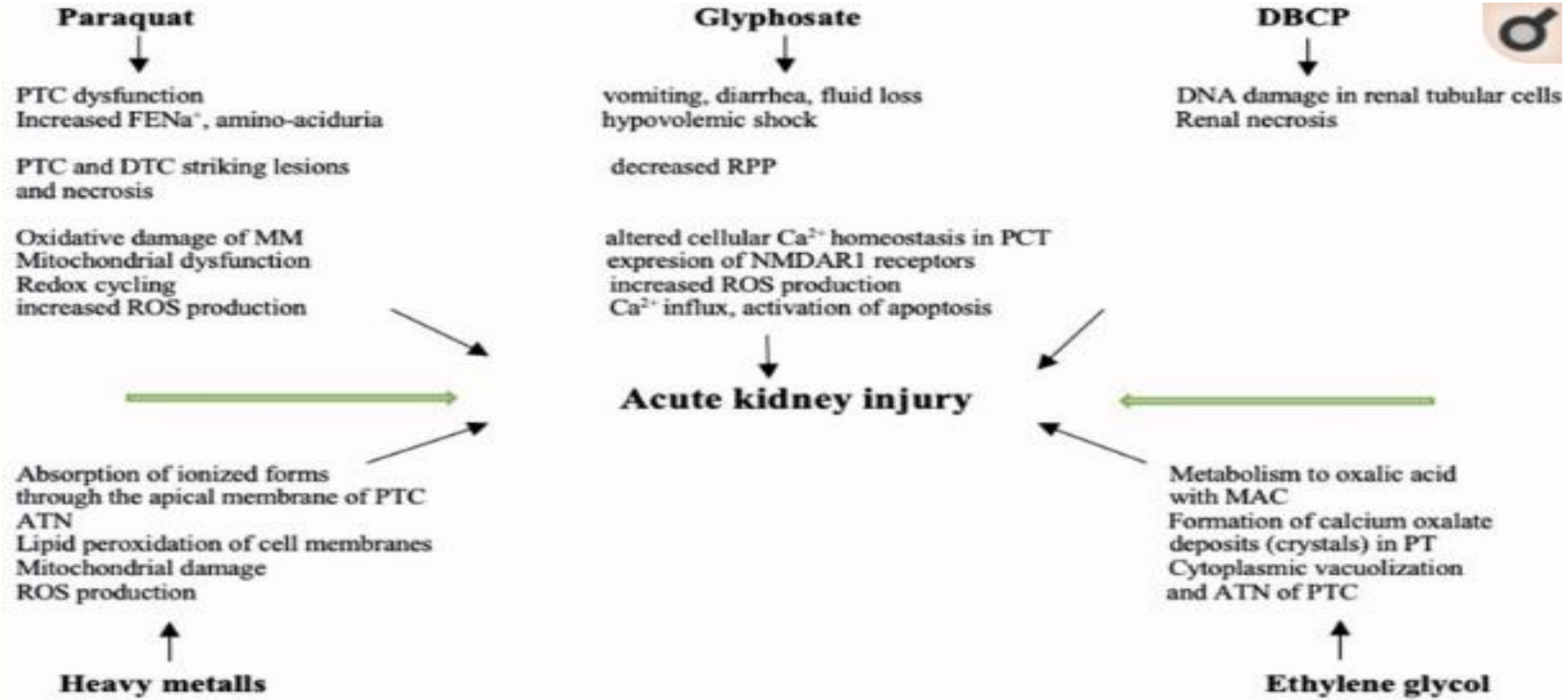


Abb: ATN – acute tubular necrosis, **DBCP** - 1,2-dibromo-3-chloropropan, **DTC** - distal tubular cells, **FENa⁺** - fractional excreti[illegible] sodium, **MAC** – metabolic acidosis, **MM** - mitochondrial membrane, **NMDAR1** - *N*-methyl-D-aspartate receptor, **PT** - proximal tubules, **PTC** – proximal tubular cells, **ROS** – reactive oxygen species, **RPP** – renal perfusion pressure

Ren Fail. 2019; 41(1): 576–594.

Illicit drug abuse nephrotoxicity

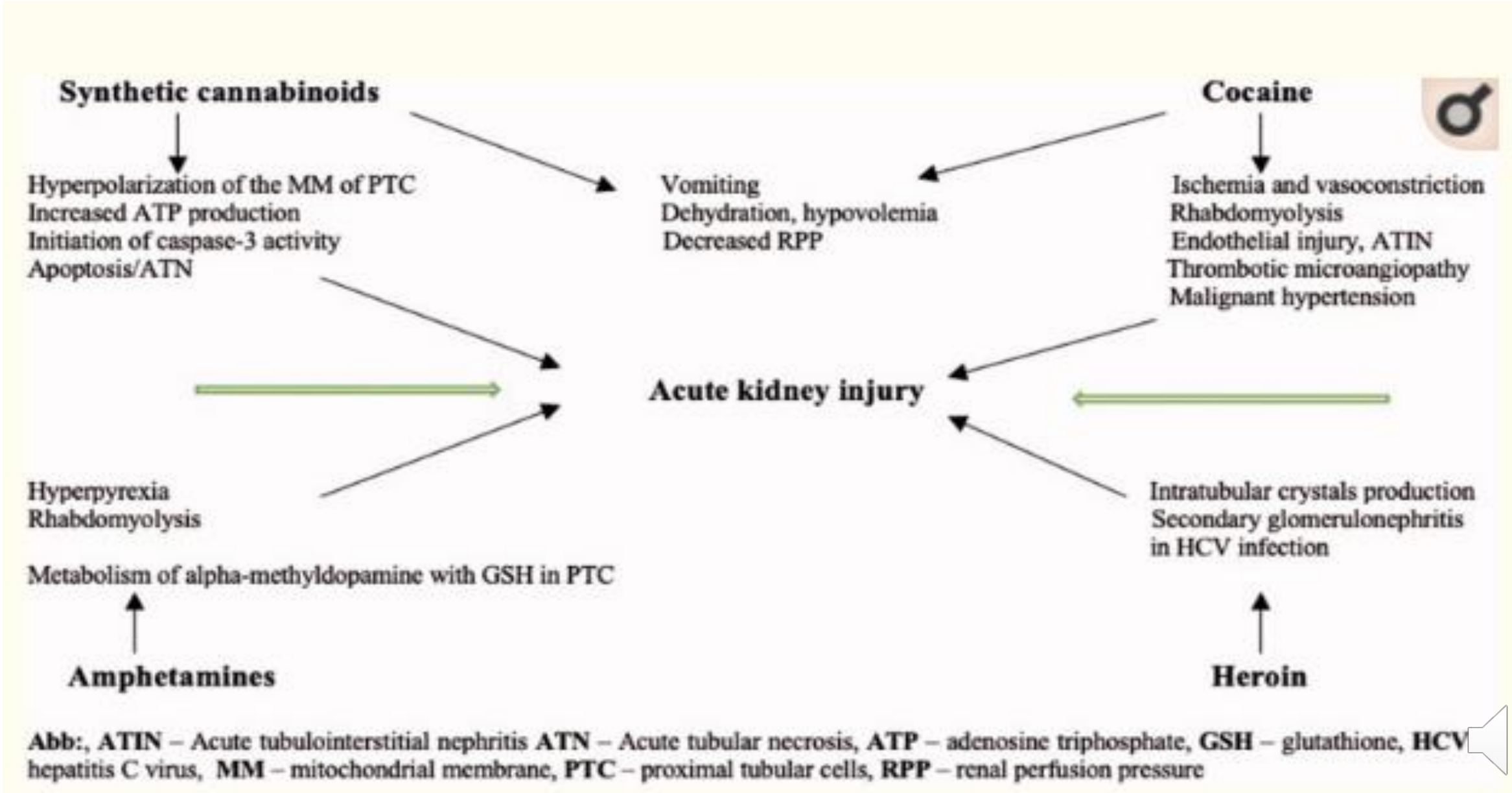


Abb:, **ATIN** – Acute tubulointerstitial nephritis **ATN** – Acute tubular necrosis, **ATP** – adenosine triphosphate, **GSH** – glutathione, **HCV** hepatitis C virus, **MM** – mitochondrial membrane, **PTC** – proximal tubular cells, **RPP** – renal perfusion pressure

REFERENCE

- ESSENTIALS OF MEDICAL PHARMACOLOGY BY K.D TRIPATHI 6TH EDITION
- BASICS AND CLINICAL PHARMACOLOGY BY KATZUNG 12TH EDITION
- PHARMACOLOGY AND PHARMACOTHERAPEUTICS BY SATOSKAR 22ND EDITION
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Thank you