Toxicological diagnosis in the critical patient: The challenge

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Abstract

Introduction: A high percentage of patients who survived to poison will be transferred to the Intensive Care Unit (ICU) to continue their management in relation to the severity of the poisoning, and possible complications that arise in this scenario. The clinical results will depend on several factors, such as the ingested dose, the characteristics of the substance, the time of medical attention, and the pre-existing state of health of the patient.

Objective: To review the clinical behavior of poisonings in the critically ill patient.

Recent findings: The data bases that yielded relevant bibliographical results were Web of Sciences, Scopus, PubMed, SciELO, and bibliographic references published between 2012 and 2020 were chosen.

Conclusions: The clinical behavior of poisonings in the critically ill patient is atypical. The intensivist must have an in-depth knowledge of the behavior and pathophysiology of the toxins since making a medical diagnosis on the

stage of the critically ill patient is challenging. The integration of all possible medical tools is required to achieve this in the absence of clinical history, and the implementation of early management strategies is necessary to reach physiological restoration by using a continuous evaluation approach. The severity of poisoning in the critically ill patient demands interdisciplinary management that includes assessment by Clinical Toxicology.

MeSH Keywords: Toxicology, blood poisoning, acute toxicity, critically ill, critical care.

Introduction

Poisoning continues to be a public health problem in the world. According to the World Health Organization (WHO), more than 900,000 people die annually from self-inflicted injuries, and particularly in Colombia, there are poisonings associated with agricultural activity, and accidental and environmental poisonings (1). The poisonings correspond to 1-3% of the income to the emergency department (2). The underreporting of cases is ostensibly high and often these patients present severe symptoms that require support management in the intensive or intermediate care units (2). It is calculated that the admission of patients to the ICU corresponds to 10-15% of the cases which generally present multiple organ failure and high risk of death due to the severity of poisoning, or other basic factors that worsen the clinical course of the patients (comorbidities). The toxicological diagnosis in settings outside the intensive care unit is largely based on the data obtained from the anamnesis, and on the findings of the physical examination, by associating the set of clinical signs with the possible agents, this process is also called toxidromes (3). The classification in toxidromes allows the clinician to quickly diagnose and identify the possible causative agent and apply an early implementation of therapeutic strategies that have an impact on the clinical results (4). However, there may be multiple agents poisoning scenarios or situations that may mask the typical clinical signs of toxidrome and confuse the clinician; particularly in the ICU setting where are confounding variables that hinder the correct toxicological diagnosis. Given the complexity of the clinical scenario, it is ideal to have a toxicology specialist to guide the identification of the agents involved (6). Interventions aimed at emerging physiological needs are the cornerstone of treatment, and in this clinical setting, not only detailed evaluation is required, but also constant reevaluation (5).

Epidemiology

Poisonings continue to be a public health problem in the world, even in developed countries with high-quality health care systems (1,7). The Toxic Registry of the United States reported in 2019 that most of the poisonings are attributed to analgesic medications (15.2%) of which acetaminophen corresponds to 58.2% of cases, ibuprofen to 12.9% and aspirin to 11.7%. In the second place, sedative poisonings such as benzodiazepines represented 53.1%. In the third place, there are opioid analgesics (10.9%), heroin represented 37.9% of the cases, followed by oxycodone with 12.4%, and fentanyl with 10.1%. Finally, psychoactive substances such as cocaine and methamphetamines correspond to only 6.2% and ethanol poisoning to 6.1% of all poisonings in that country in spite of the high underreporting that also occurs in this regard.

A high percentage of patients require in-water resuscitation during their care (70.2%), ventilatory support and cardiovascular support (25.5%), advanced toxin removal therapies (24.8%), and renal support therapy (43.4%) as well as ICU stay. A mortality percentage of 0.9% was reported from a total of 7.043 patients registered in the record (8). In underdeveloped countries, pesticide poisoning for agricultural use is more frequent, reaching up to 20% of fatal events, compared to 0.5% of drug fatalities in industrialized countries (9). Furthermore, in Latin America and the Caribbean, it is considered that there is underreporting of poisonings (1). Thus, The Pan American Health Organization (PAHO) reports that exposure to chemical contaminants continues to be an issue that is not given enough attention to (10). In 2017, the national incidence of poisoning was 80.6 cases per 100,000 inhabitants (11) and according to the toxic report of the National Institute of health (12), in Colombia the notification trend has been increasing. In general, the consumption of chemical substances for autolytic purposes is mainly found in young adult patients while accidental poisoning occurs mainly in older adults or children (7). The timely diagnosis, especially the early intervention guided by the symptoms of the intoxicated patient, can improve the clinical results (13).å

Toxicological syndromes (Toxidromes)

The order of toxidromes presentation goes as follows: The sedative-hypnotic is the more frequent with 10.8%, followed by the anticholinergic with 6.6%, then, the sympathomimetic with 4.7%, the opioid with 3.8%, and finally, the syndrome cholinergic corresponding to only 0.7% of cases (8).

A toxidrome is a set of clinical signs and symptoms typical of certain specific xenobiotics with similar mechanisms of action. Toxidromes are a navigation chart for the clinician, who can carry out the differential diagnosis within the multiple potentially causative toxic agents through physical examination, and also, provide a guideline for taking laboratory tests and treatment (14).

Poisonings are commonly found in critical medicine and intensive care either by accidental exposure (occupational, adverse drug reactions, accidents at home) or intentional exposure (suicide attempt or substance abuse). All patients with confirmed or suspected toxicity should be managed preventively by providing the necessary supports, identifying the causative agent, and finally, supplying the antidote if applicable (15). Some toxidromes have similar characteristics and are not fully presented as described in the literature, which can be confusing when making the diagnosis, so it must be carefully evaluated and inquired with the patient or companions (3). The description of the different types of toxidromes is presented below:

1. Anticholinergic

This is a toxidrome that occurs due to side effects of psychiatric medications or anesthesia, involuntary intoxication, or intoxication of criminal origin with drugs with anticholinergic activity. Medicines or substances with anticholinergic action act by inhibiting muscarinic receptors and consequently, inhibiting the action of acetylcholine. Muscarinic receptors are associated with the parasympathetic nervous system, which is located in different organs and systems such as the skin, eyes, heart, respiratory system, bladder, and gastrointestinal tract (3).

Pathophysiological speaking, anticholinergic agents act as competitive antagonists against acetylcholine at the level of the muscarinic receptors, produce a decrease in the activity of acetylcholine and finally, decrease the release or synthesis of it (3). The typical clinical manifestations of these anticholinergic agents are mydriasis, redness of the skin, delirium, anhidrosis, and hyperthermia; however, to carry out a systematic review on physical examination, the manifestations are divided into central and peripheral. The symptoms of central origin that appear are confusion, restlessness, apprehension, speech difficulties, agitation, hallucinations and in more serious cases, even stupor and coma (16). The peripheral type symptoms can be mydriasis, blurred vision, photophobia, tachycardia, arterial hypertension, sometimes arrhythmias such as flutter or atrial fibrillation, atrioventricular

blocks (AV blocks), supraventricular tachycardia, and even QT prolongation. At the respiratory level, there are findings of tachypnea and dryness at the nasal level. In terms of gastrointestinal symptoms, these are characterized by oral dryness, dysphagia, and ileus, the latter is identified as one of the most common complications and predictors of greater mortality and a longer stay in the ICU (17). At the urinary level, there is urinary retention, neuromuscular tremor or clonus, and in cases with greater involvement, there is presence of rhabdomyolysis. Dryness is observed in the mucous membranes, as well as in the skin, which can be better evidenced in the areas where the greatest number of sweat glands are concentrated and consequently, it leads to hyperthermia due to the inability to sweat and also thermoregulate the heat of the body.

2. Cholinergic

Acetylcholine is a neurotransmitter found throughout the nervous system, including the Central Nervous System (CNS), the autonomic ganglia (sympathetic and parasympathetic), the postganglionic system of the parasympathetic nervous system, and the motor endplate of skeletal muscle. Acetylcholine is the neurotransmitter that binds and activates the muscarinic and nicotinic receptors, and in turn, the enzyme acetylcholinesterase (AChE) regulates the activity of acetylcholine within the synaptic cleft (3).

Acetylcholine binds to the active site of AChE where the enzyme rapidly hydrolyzes acetylcholine to choline and acetyl; subsequently, these hydrolyzed products rapidly dissociate from AChE so that the enzyme is free to act on another acetylcholine molecule, but the AChE inhibitory substances like organophosphates and carbamates, prevent the inactivation of acetylcholine, generating overstimulation with acetylcholine (18).

The clinical manifestations generated by this toxidrome are affected in all systems since both muscarinic and nicotinic activated receptors lead to sympathomimetic system activation and stimulation of the neuromuscular plate junction. In view of this, hyaline rhinorrhea, salivation, bronchorrhea, bronchoconstriction, and cough, which clinically manifests wheezing and an increase in the expiratory phase, occur at the respiratory level. In the cardiovascular system, the manifestation is given by decreased activity due to bradyarrhythmias and hypotension. Additionally, at the level of the skin and the sweat glands, there is presence of tearing, blurred vision, meiosis, and diaphoresis (18). Furthermore, the cholinergic innervation in the gastrointestinal system causes an increase in the intestinal motility and

relaxation of the reflex tone of the anal sphincter; this results in salivation, increased intestinal motility, nausea and emesis, crampy abdominal pain, watery salivation, and gastrointestinal hyperactivity with symptoms such as nausea, vomiting, tenesmus, and diarrhea. The cholinergic stimulation of the detrusor muscle of the bladder causes contraction of the urinary bladder and relaxation of the muscles of the trigone and sphincter resulting in involuntary urination (18).

Seizures are frequently seen in severe cholinergic poisonings due to effects of the excess of acetylcholine in CNS. The stimulation of nicotinic receptors on the motor plate may initially lead to twitching but these may rapidly progress to flaccid paralysis. The tendency to cause seizures, as well as paralysis, puts cholinergic patients at risk of a non-convulsive epileptic state (3,14)

Organophosphate-type insecticides can produce a clinical entity called the intermediate syndrome, which is characterized by proximal paralysis of the cranial nerves, the flexor muscles of the neck, and the breathing muscles between 24 to 96 hours post-intoxication (19, 20). The mechanism by which this occurs is not well clarified; however, some studies suggest that there is a decrease in AChE and the expression of the nicotinic acetylcholine receptor (nAChR) and mRNA, in addition to increased oxidative stress and alteration of the neuromuscular plate at the postsynaptic level (18).

3. Sympathomimetic or adrenergic

Norepinephrine is the neurotransmitter that acts at the level of β1, β2, α1 and α2 adrenergic receptors, which are found in fibers that innervate the skin, eyes, heart, lungs, gastrointestinal tract, exocrine glands, and some neuronal segments in the central nervous system (CNS). The physiological response to stimulation and activation of the sympathetic nervous system produces CNS excitation (agitation, anxiety, tremors, delusions, and paranoia), tachycardia, seizures, hypertension, mydriasis, hyperpyrexia, and diaphoresis (21). In severe cases, cardiac arrhythmias may occur and may even lead to coma. The etiology of this type of toxidrome is given by abuse of substances such as cocaine, amphetamines and their derivatives (MDMA, methamphetamine), designer drugs (e.g mephentermine, mephedrone), and drugs such as ephedrine, pseudoephedrine and caffeine (21).

4. Opioids

The abuse of the prescription of opioids and the increase in illicit sales have created what is colloquially known as the opioid epidemic, and

consequently the increase in poisonings by this type of agent (22). Opiates are naturally narcotic derived from opium, which are isolated from the poppy plant. Some of these are semi-synthetic compounds such as morphine and codeine, and others are synthetic compounds such as hydrocodone, hydromorphone, oxycodone, methadone, and fentanyl (22).

All of these medications have potent sedative analgesic properties, but they all have different pharmacokinetic properties depending on their three main classes of opioid receptors: mu (m), kappa (k), and delta (d); or OP3, OP2, and OP1, respectively. Several of these opioids have different affinity profiles for opioid receptors, which explain the differences in clinical effects (14).

Opioid poisoning may present generalized clinical manifestations depending on the agent used, dose, method of administration, and presence of other drugs or substances of abuse. The classic toxidrome consists of myosis plus respiratory depression (hypoventilation, bradypnea), and depression of the central nervous system. There is also a decrease in intestinal motility (14), which is expressed on physical examination as a decrease or absence of bowel sounds, hypotension, and hypothermia (22).

5. Serotonergic

Some opiates such as fentanyl, meperidine, methadone, codeine, tramadol or oxycodone, selective serotonin, and norepinephrine reuptake inhibitor antidepressants, yagé, and some antiparkinsonian agents may produce serotonin syndrome, which consists of increased serotonin concentrations in the central nervous system, a neurotransmitter responsible for regulating mood, social behavior, sleep, memory and even digestion (23) The classic triads consist of neuromuscular excitation (hypertonia, tremor, spontaneous or inducible myoclonus, hyperreflexia), excitation of the autonomic nervous system (tachycardia, hyperthermia, mydriasis, diaphoresis, nausea, diarrhea) and altered state of consciousness (agitation, confusion). In some severe cases, the symptoms can include rigidity, respiratory failure, coma, and severe hyperthermia (24).

6. Sedative-hypnotic

The hypnotic sedative drugs are CNS depressants such as benzodiazepines, barbiturates, and ethanol. The chronic use of these substances can develop tolerance, and the abrupt cessation or reduction in the amount of these drugs can precipitate a life-threatening withdrawal syndrome (25). It is manifested by the deterioration of the state of consciousness with different

intensity variables (clouding, stupor, coma), miosis (with slow response to light), hypothermia, respiratory compromise (bradypnea, respiratory arrest) and cardiovascular affections (hypotension, bradycardia, cardiac arrest) (3).

7. Hallucinogen

Hallucinogens can cause a variety of physical and psychological manifestations. Among the symptoms that can occur, hallucinations, psychosis, agitation, perceptual distortions, depersonalization, derealization, muscle hyperactivity, synesthesia, seizures, hyperthermia, and mydriasis are the most common (26).

What is the clinical behavior of poisoning in the critical patient?

Patients with exogenous intoxication in the ICU do not have a well-established clinical course; furthermore, their complications are not predictable and when it comes to typifying a toxicological emergency, the uncertainties are greater concerning other pathologies treated in the ICU. The clinical history is usually not reliable, hindering the application of adequate therapies and antidotes for the patient. Thus, the relevance of recognizing potential complications early, and intervening early as well, is one of the priorities for the management of critically intoxicated patients. The most crucial action is the monitoring of clinical patterns, rather than a specific management that sometimes cannot be performed. Some poisonings may be initially asymptomatic (sustained-release drugs), and it subsequently presents deterioration of the physiological variables in a rapidly progressive manner, and it is sometimes not identified in a timely way (27). The implementation of therapies aimed at reestablishing physiology allows, on the one hand, to gain time while identifying the etiology of the condition, and on the other hand, help to minimize the morbidity and mortality associated with late management.

The clinical manifestations are varied and may be related to the patient's general health and comorbidities. These factors could mark the response to a stressor that is in this case, given by the effects of the xenobiotic, which make it difficult to characterize the population from the clinical point of view (14). There is no typical pattern expressed by intoxicated patients in critical condition, and in this sense, the intensivists must carry out an approach for toxidromes. As it was previously mentioned, the manifestations are varied and are given by effects derived from the toxic non-intervened or inadequately intervened pathophysiological consequences. In this sense, the natural course can evolve into a critical condition that includes neurological

compromise, circulatory instability, and multi-organ failure leading to death. These are common effects in this group of patients regardless of the xenobiotic that caused the condition, which deserve management in the intensive care unit (28). The clinical behavior of poisonings in the critically ill patient could be grouped according to the consequences of the toxidromes reviewed in advance; thus, a patient with exogenous intoxication has a potential risk of multiple complications, including the following conditions (5,29):

a. Respiratory failure: A cholinergic toxidrome may present hypoxemic, hypercapnic, or mixed respiratory failure, characterized by sialorrhea and bronchorrhea, depressed neurological state, or muscle weakness due to motor plate compromise. A deterioration in the muscular strength necessary to generate adequate airflow finally compromises hematosis (the exchange of gases). In an opioid toxidrome, there is a significant deterioration of the sensorium, which compromises the protective capacity of the airway (2).

b. Shock state: In the case of cholinergic manifestations, the origin may be mixed, specifically; hypovolemic due to intestinal and extraintestinal losses typical of his condition, as well as a cardiogenic component given by bradycardia. Unlike opioid and hypnotic-sedative toxidrome, in which the main mechanism is distributive given the loss of sympathetic tone of the circulatory system. Furthermore, multiple xenobiotics can impair the patient's heart rhythm, that is why an electrocardiographic study is essential and mandatory in this population (2).

c. Hypertensive emergency: Target organ involvement may occur mainly over the central nervous system in anticholinergic, sympathomimetic, and serotonergic toxidromes, and it is given by an increase in the pressor response outside the range of self-regulation of blood pressure, supported by a state of psychomotor agitation. Reason why, an adequate control of its neurological condition and systemic vascular resistance are necessary for the Intensive Care Unit (2).

How to make the diagnosis in the critical patient?

Making the diagnostic approach to the intoxicated patient in the ICU raises a challenge for the intensivist since on many occasions the critically ill patient is not able to provide information that contributes to making the diagnosis of poisoning. As previously mentioned, the diagnosis depends largely on the anamnesis, a process in which it is possible to obtain information on the type of toxic ingested, the amount, the time, and the answers

to the questions: how was the contact? Where did it occur? Why did it occur? Is it the first time it occurs? Are there various substances involved? What history of illnesses does the patient have? Does he/she present use of medications, chemicals or other substances? (30). If the patient is admitted to the ICU with all the complete information collected from the emergency department, the therapeutic approach continues according to the available antidote protocols (30). However, some patients enter the ICU with unclear symptoms, with an incomplete medical history and with a diagnosis of poisoning made through suspicion, by matching the symptoms or findings that are compatible with toxidromes (2,5). In terms of toxicological testing, there exists limitation that if the samples are taken outside the window period, they can come out falsely negative (5), and this is why the toxicological diagnosis in the critically ill patient is a challenge. The following case is an example of a patient who entered the ICU under the influence of sedoanalgesia, intubated, and without information on his condition, whose toxicological process and etiology were diagnosed after receiving a thorough evaluation. (2).

Case 1

A 36-year-old male patient, with a history of epilepsy, was found on the public highway with a seizure status, he was administered with benzodiazepines and when faced with refractoriness crisis, orotracheal intubation was performed. At the moment of admission, the patient was hypertensive, mydriatic, presented tachycardia, and was under the effects of sedoanalgesia. Normal results were found when conducting a simple skull tomography. He was initially treated in the ICU with suspicion of seizure status and considering hypertension and tachycardia secondary to it. An electroencephalogram was conducted after 36 hours without seizure activity, but still with circulatory instability and irregular evolution. Toxicological tests were carried out with positive results for amphetamines and meta-amphetamines.

In this case, we can infer that intoxication was not the initial diagnosis, and given the multiple confounding factors, and even the overlapping of the base pathology and various substances consumption, the evaluation for toxidromes was challenging. The intensivist should then initially ask the critically ill patient without complete information on the condition, whether he is intoxicated or not. This question should be asked whenever we are dealing with a patient with an unclear diagnosis, with an irregular clinical

evolution, with typical clinical signs (stigmata of venipuncture, trauma), and in this sense, a permanent evaluation and re-evaluation is required. The performance of toxicological laboratory studies, images, or sometimes, when there is no toxicology laboratory, late results, or false negatives given if the samples were taken outside the window period, the diagnosis may be made by evaluating the clinical response to empirical management. The recognition of patterns is not typical in the critically ill patient, thereby the clinical and paraclinical diagnostic tools must be integrated when facing high levels of suspicion. Additionally, an adequate interpretation of the constellations of signs and symptoms must be done since toxidromes can also appear partially or mixed if several substances are involved, which may mask the findings (2). All critically ill patients require an initial and serial electrocardiographic study to determine QRS abnormalities, QT abnormalities, or classic signs of certain toxins ("digitalis cuvette", which is a decrease in the ST segment of concave shape). Table 1 summarizes some of these findings and causal agents (2).

Table 1. Electrocardiographic Findings in Poisonings

Arrhythmias	Tachyarrhythmia, bradyarrhythmia, ventricular arrhythmias
QRS ANOMALIES	Long QRS: Tricyclic antidepressants.
QT ANOMALIES	Fluoroquinolones, ondansetron, macrolides, arsenic, haloperidol, tricyclic antidepressants, trazodone, methadone, cocaine, amiodarone.
CLASSIC SIGNS	Digoxin; digitalis cuvette.

Adapted from Brent, J et al. (2)

Multiple xenobiotics can deteriorate the acid-base and electrolyte state that develop neurological manifestations and compensatory responses that demand ventilatory support (28). It is necessary to carry out an arterial gas test since it allows general practitioners to assess the severity of the poisoning, evaluate perfusion disorders, and make a specific diagnosis for some substances. The structured approach allows evaluating the primary disorder (acidosis/alkalosis; metabolic/respiratory) if there are secondary disorders, evaluation of the anion gap to rule out, or confirm poisoning. On one hand, when there is elevated AnionGap (>12mEq/L), poisoning by ASA (Acid acetylsalicylic), ethanol, and methanol, ethylene glycol is suspected. On the other hand, when the AnionGap is normal (8-12 mEq/L), poisoning by carbonic anhydrase inhibitors or ion exchange resins is suspected (5). Some laboratory tests such as lactate levels, transaminases, OsmolGap, electrolytes, serve to guide possible etiological agents. Table 2 describes the laboratory findings related to poisoning (2).

Table 2. Laboratory findings related to poisoning

Hyperlactatemia	Carbon monoxide, cyanide, or methanol.
Sodium levels	SIADH*; Selective serotonin reuptake inhibitors (SSRIs) Diabetes insipidus; Lithium
Arterial gases: HYperchloremic acidosis	Topiramate
Potassium levels hypokalemia	Methylxanthines
Nitrogen containing compounds	Ethylene glycol, acetaminophen, cocaine. Rhabdomyolysis (antipsychotics, neuroleptic malignant syndrome, sympathomimetics, opioids.)
Transaminases coagulation times	Acetaminophen. Hepatotoxins (plants, essential oils, herbal supplements, over-the-counter and prescription medications, halogenated hydrocarbons.
OsmolGAP	Alcohol poisoning

*SIADH (Syndrome of inappropriate antidiuretic hormone secretion)

Adapted from: Brent, J et al 2. Kent R et al13 Zarbock A et al. (33).

Toxicological tests can be done in blood or urine, and it is preferable to carry out the first tests with quantitative levels. It should always be evaluated whether they alter the course of the disease or change its behavior since it has been described that the performance of tests only modifies treatment in 15% of cases (2,14). It is considered that they should be performed within 1-5 days of the onset of symptoms; however, this varies according to the substance (30,31). Table 3 summarizes the main toxics and their window to obtain a reliable result.

Table 3. Window time for toxic detection.

Substance	Detection window time	Commentary
Amphetamines	2 days.	False positives.
Barbiturates	< 2 days. 1-week phenobarbital.	
Benzodiazepines	2-7 days* variable.	Does not detect lorazepam, alprazolam, new.
Cocaine	2 days.	Detects benzoylecgonine metabolite.
Ethanol	< 1 day	
Marijuana. Tetrahydrocannabinol THC	2-5 days. > chronic use.	
Opioids	2-3 days.	Synthetics often do not detect. Separate methadone test.

Adapted from de Kent R et al13 Zarbock A et al. (33)

Currently, there is the availability of panels that sense 40-100 substances; nonetheless, those that are analyzed are 80% of poisoning cases. In the ICU patient, the taking of toxicological samples will depend largely on availability and the speed with which the results are received, which would both change the behavior and are ultimately not routinary.30. Its taking will then be linked to the clinical context at the time the patient takes his initial picture, and to the need of clarification in the diagnosis and the implementation of advanced care measures, or to cases of illegal situations in which documentation of the toxic is required for legal reasons. 2,5,31. The practical approach to the intoxicated patient in the ICU is in the flowchart (Figure 1).

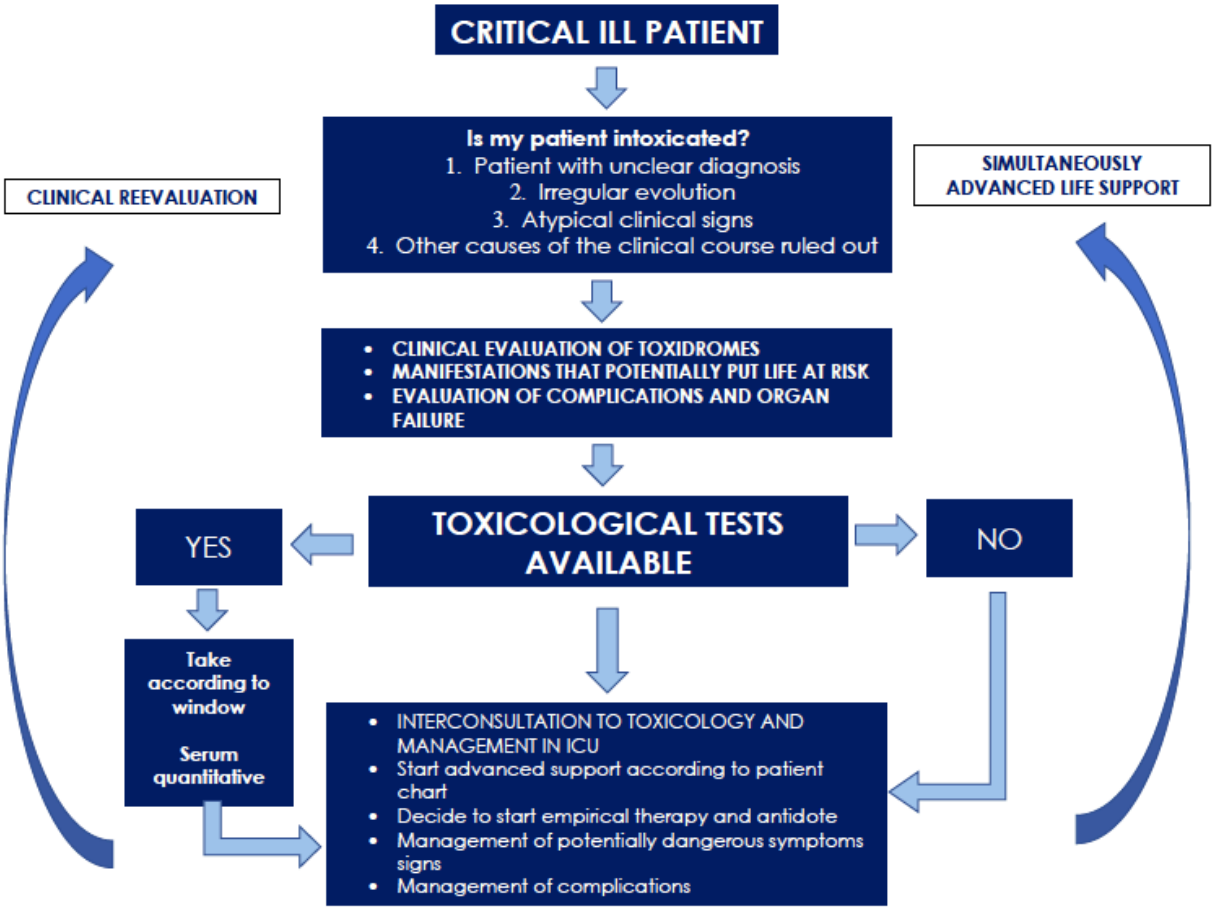

Image realized by the authors, based on references: Brent, J. et al. (2); Rasimas J, et al. (5); Thompson TM et al. (14)

Finally, images have limited the diagnostic value in this clinical setting. An x-ray can be done to evaluate for iron and lead poisoning, an abdominal and pelvic tomography can be conducted to evaluate caustic poisoning,

packaged medications, and foreign bodies (criminal behaviors), and a simple skull tomography can be implemented for making alternative diagnoses in terms of chain inhibitor poisoning transporter of electrons that produce heart attacks in the area of the basal ganglia. But, in general terms, they are not a priority (5).

What therapeutic interventions are indicated in the ICU?

The treatment of poisoning depends on the agent involved, the general measures that include the ABCD within the protocol of the intoxicated patient, and specific antidotes are described in the current guidelines. Gastric lavage is usually not indicated, and a single dose of activated charcoal can be administered if the intake is recent (<1 hour) depending on the type of poisoning and whether or not there are contraindications (30).

The implementation of early support therapies has a positive impact on both in-hospital stay, as well as in costs of care and mortality (5). It is considered essential to carry out an orderly approach to the patient taking into account the maintenance of the airway, oxygen therapy and permanent observation of the respiratory muscles' activity, and to perform early orotracheal intubation if the respiratory failure is detected. The circulation refers to the phenomenon of hypotension and arrhythmias that were mentioned in the clinical manifestations and that are susceptible to intervention, either with vasoactive support or with pacemaker implants urgently, it depends on the case of the patient (2). Table 4 summarizes the main toxics with their available antidotes.

Table 4. Main antidotes for the management of the most common poisonings.

Antidote	Indication
N- acetylcysteine	Acetaminophen
Atropine	Cholinesterase inhibitors
Absolute alcohol 96% or vials of brandy 29% for oral use	Methanol, ethylene glycol, or sodium fluoroacetate
Antivenoms	Snakebite (PROBIOL freeze-dried anticoral serum, multipurpose anticoral serum, polyvalent antifungal serum) and alacram (BIOCLON lyophilized antialacran serum)
Methylene blue	Symptomatic methemoglobin or ≥30%
Prussian blue	Radioactive thallium or cesium poisoning
Sodium bicarbonate	Tricyclic antidepressants
Deferoxamine	Iron poisoning
Dimercaprol (BAL)	Arsenic
DMSA (Succimer)	Lead, arsenic and mercury salts
Fag Shards	Colchicine
Physostigmine	Severe anticholinergic syndrome
Flumazenil	Respiratory depression by benzodiazepines
Glucagon	Beta-blockers
Calcium gluconate	Calcium channel blocker poisoning
Naloxone	Opioid respiratory depression
Amyl nitrite	Cyanide
Thiamine	Prevention or treatment of Wernicke-Korsakoff encephalopathy in alcoholics
Protamine	Reverse anticoagulant effect of unfractionated heparin
Pralidoxime	Nicotinic and muscarinic syndrome secondary to cholinesterase inhibitor poisoning
Vitamin k	Warfarin or superwarfarins

Adapted from Thompson TM et al. (14); Flanagan RJ et al. (41); Peña LM et al. (42)

Patients with acute kidney injury secondary to shock, or for poisoning may require renal replacement therapy (32-36). Dialysis is recommended in alcohol poisoning with severe metabolic concentration, serum methanol, and ethylene glycol concentrations greater than 50 mg per deciliter (methanol, 16 mmol per liter; ethylene glycol, 8 mmol per liter), if there is a deterioration of vital signs despite management, visual disturbances (associated with methanol poisoning,) or acute kidney injury (37). Intermittent hemodialysis

removes toxic alcohols more quickly than continuous renal replacement therapy. Depending on the redistribution of alcohol, the metabolites or both may require repeated dialysis (38).

Extracorporeal toxic agent removal therapy represents a treatment modality that promotes the elimination of exogenous toxins and temporarily supports or replaces vital organ function. The various principles that govern the elimination of the toxic through this therapy (diffusion, convection, adsorption, and centrifugation) and how the components can be adjusted to maximize the elimination have been discussed, these are aspects that the intensivist must take into account when implementing this therapeutic tool (39). Indications suggest that there is an exposure to the toxin that causes serious morbidity and mortality, the toxicity cannot be treated with an antidote. Thus, the implementation of endogenous toxic clearance of less than 4ml / min/kg, or volume of distribution <1-2 L / kg must be conducted.

A document was recently published by the International Society of Nephrology (39), which indicates a diagnostic algorithm based on the characteristics of the toxin for therapeutic decision-making. According to the percentage of protein binding of the toxin at the current concentrations during the evaluation, it is indicated that if the percentage of protein binding is greater than 95%, the use of plasma exchange therapies (plasmapheresis) is favorable, and if the binding percentage is 80%, hemoperfusion therapies are preferred. When the molecular weight is 15,000 Da, the therapy of choice is high-flow hemodialysis, if it is 15,000-25,000 Da, the recommended option is hemofiltration, if it is 25,000-50,000 Da, continuous hemodialysis or hemoperfusion are advised, and in a molecular weight greater than 50,000 Da, plasmapheresis is suggested. Recommendations are made for conducting extracorporeal therapy in cases of poisoning caused by barbiturates, lithium, methanol, metformin, salicylates, thallium, and valproate. Besides, it is recommended to apply neutral ions for treating poisoning by phenytoin, poisoning by acetaminophen and carbamazepine, and poisoning by tricyclic antidepressants and digoxin (40).

What complications are the most frequent?

The main complications can be triggered by intoxication or due to exacerbation of the patient's underlying pathologies. Respiratory failure, aspiration pneumonia, shock, multiple organ dysfunction that include liver failure and acute kidney injury requiring advanced therapy, cardiorespiratory arrest, and neurological sequelae are complications that lead to ICU stay or

death. In view of the aforementioned, the prognosis will not depend solely on the type of poisoning, but rather on the consequences derived from it and its management (2,5).

Conclusions

A percentage of patients who survive to poisoning will be transferred to the Intensive Care Unit to continue their management in relation to the severity of the poisoning and possible complications that arise in this scenario. The clinical results will depend to a great extent on numerous factors, such as the ingested dose, the characteristics of the substance, the time of medical attention, and the pre-existing state of health of the patient. The clinical behavior of poisonings in the critically ill patient has a neurological and circulatory predominance, supported by acid-base, electrolyte, and heart rhythm compromise secondary to different xenobiotics that require monitoring and advanced management in the ICU. The intensivist must have an in-depth understanding of toxic behavior and pathophysiology since making a toxicological diagnosis is challenging. The integration of all possible tools is required to achieve this in the absence of medical history, and the implementation of early management strategies to restore physiology using a continuous evaluation approach is necessary. The severity of the intoxication in the critically ill patient demands interdisciplinary management that counts in addition to the evaluation of clinical toxicology.

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