Chapter

Poisoning in the Pediatric Intensive Care Unit

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Abstract

Poisonings during childhood (both accidental and voluntary) are a common cause of presentation in the emergency departments (EDs) and the pediatric intensive care unit (PICU). The admission to PICU is warranted both for treatment and for continuous monitoring, as sometimes the evolution of a poisoning could be unpredictable. Sometimes, complications arise that may prolong the patients' hospitalization and may contribute to lowering the survival rate. The staff in these departments must be well trained to ensure patient monitoring, early detection of complications, and rapid intervention. Supporting vital functions is the main objective of the management of a poisoned patient admitted in PICU. In recent years, staff competence and advanced medical technology have helped to improve the prognosis of the patients admitted to these departments, including of the poisoned patients.

Keywords: intensive care, poisoning, children

1. Introduction

Poisoning is a relatively common medical emergency worldwide and raises particular problems of diagnosis and treatment especially in children, regardless of the path the toxic enters the body (ingestion, inhalation, injection, or skin absorption). This age group is the most vulnerable population with the highest risk of accidental intoxications that can be partially prevented [1]. It is a common cause of presentation in the ED and the PICU. Early identification of the clinical characteristics of patients with acute intoxication and rapid initiation of therapy in these services can help reduce the mortality of intoxicated patients [2, 3]. These departments have the ability to continuously monitor vital parameters, use the most advanced medical technology and the most appropriate treatment. Usually, admission to PICU is by ED or by transfer from another hospital [4]. Often, a poisoned patient will be brought into intensive care not for treatment, but for continuous surveillance and monitoring in order to minimize mortality. On the other hand, care in these units has a very high cost. It is therefore recommended that the admission of poisoning cases in intensive care should take into account the efficient use of resources without compromising patient care [5]. The percentage of children with acute poisoning in PICU ranges from 8% [6] to 11.7% [2]. In the United States in 2014, 2336 intoxicated patients admitted to intensive care units needed ventilatory support, 509 received vasopressors, and 127 needed hemodialysis [4].

2. Admission of intoxicated patients in PICU

There are several studies that attempt to establish criteria for admission to intensive care in patients based on severity scores (APACHE II/III, PRISM II/III, SAPS II, Glasgow etc.). These included patients with various medical and surgical conditions, but few can be validated using such scoring systems in poisoned patients [7–9]. Until more specific poisoning factors are established, it is thought that experience and proper clinical judgment can predict which patients will receive intensive care. The presence of certain abnormal symptoms or abnormal test results may require monitoring and/or treatment in PICU regardless of the suspected toxic. This approach is more consistent with the principle of "treating the patient and not the poison" [5]. It should be kept in mind that an initially asymptomatic poisoned patient may worsen later. Poisoned children and adolescents should be directed to the nearest intensive care unit that has pediatric critical care practitioners and equipment appropriate to pediatric age.

2.1 Criteria for admission to intensive care of the poisoned patient

I. Acute respiratory failure characterized by one or more of the following [4]:

- Need for ventilatory support or emergency tracheostomy.
- Marked respiratory compromise as indicated by:
  a. FR <20 or >60 for children <1 year and <12 or >60 for children >1 year.
  b. SpO_2 <92% when O_2 is administrated by mask or tracheostomy.
  c. PaO_2 <80 mm Hg at 100% O_2 administrated by mask.
- Rapidly progressive deterioration in respiratory status.
- Respiratory acidosis with $PaCO_2$ > 60 mmHg and pH < 7.25.
- Airway obstruction, apnea, anaphylaxis.

II. Hemodynamic instability or circulatory insufficiency characterized by one or more of the following:

- Shock as indicated by capillary refill time >4 s, distal or proximal nonpalpable pulse, systolic TA < lower age limit or TA < mean 50 mmHg (<40 mmHg in newborn), metabolic acidosis with < pH 7.25, base deficit >10 or serum bicarbonate <10 mEq/l, need for invasive hemodynamic monitoring.
- Cardiac instability and arrhythmia, necessity of continuous perfusion or vasoactive substances, ECG ischemic changes, congestive heart failure, and vascular volume instability.

III. Neurological instability manifested by one or more of the following:

- Neurological damage with one or more of the following: Glasgow score <10, severe irritability, hallucinations, and change of posture.
- Intracranial bleeding, increased intracranial pressure, seizures, or delirium.

IV. Severe metabolic disorders: serum Na <125 mmol/l or >160 mmol/l, serum K <3 mmol/l or >6.5 mmol/l, glucose <30 mg/dl or >400 mg/dl, ionic calcium <0.8 mEq/l, base deficit >−10.

V. Other patients at risk of organ failure or system failure.

VI. Toxic exposed patients in which none of the above are present but:

- Within a few hours, one of the above criteria is expected.
- Suicide patient that cannot be monitored in other unit care.

3. Specific monitoring and treatment in PICU

The main concern in the management of a patient with acute intoxication in PICU is the support of the vital functions. The general measures in a poisoned patient do not differ significantly from those required in a patient admitted to PICU with similar symptoms and a comparable level of severity but with pathology [4]. These critically intoxicated patients should be rapidly recognized by the clinician and evaluated for appropriate therapy. Continuous follow-up of vital functions, neurological status, blood volume, and heart rate makes possible early detection of poisoning worsening signs requiring rapid intervention to prevent complications [5]. Advanced medical technology in PICU offers a number of invasive and noninvasive options that can trigger an early warning of rapid deterioration or provide feedback about the response to treatment. For example, monitoring hemodynamic parameters are valuable for managing poisoned patients with hypotension, volume depletion, or respiratory failure from acute lung injury (ALI). Most importantly, clinicians need to recognize that no monitoring device improves clinical outcome unless is completed by a treatment.

Some antidotes and specific therapies are initiated in ED and continued in PICU, which is the most appropriate place to administer or continue treatment. In addition to conventional therapies, PICU's medical practitioners also know how to deal with situations that do not look like treatment protocols. For example, high doses of atropine, like hundreds of milligrams, can be used to treat organophosphate insecticides [5, 10]. Sometimes the antidote has less effect than the toxin. For example, opioid-intoxicated coma patients responding to naloxone are rapidly recovering. But these patients should be closely monitored for rejoining their coma, and in this situation, the antidote should be repeated. A surveillance period of at least 2 h after the last dose of naloxone is required to assert that the risk of recurrence of toxicity has passed [11].

Pulse oximetry is the recommended method to detect the presence of hypoxemia and to guide the administration of oxygen. Gasometry is a more accurate method for highlighting hypoxemia [4].

4. The poisoning effects on specific organ systems

4.1 Acute respiratory failure

Acute respiratory failure is a common condition for children with various intoxications to come into the PICU. Respiratory failure occurs due to central hypoventilation, central nervous system depression, by the poisoning of central nervous system

depressants (barbiturates, opiates, alcohol, and tranquilizers), intoxication with organophosphate compounds, alkaloids, and atropine. Respiratory muscular paralysis is another mechanism encountered in hemlock poisoning (*Conium maculatum*) and organophosphate. Mechanical ventilation disorders may occur during toxic seizures [12, 13]. Airway obstruction through laryngeal edema is another mechanism of acute respiratory failure encountered in poisoning with corrosive or toxic acidic and toxic bases that cause anaphylactic shock, and obstruction through hypersecretion may occur in intoxication with sympathomimetic substances or organophosphate compounds. Acute toxic respiratory failure may also occur with acute pulmonary edema in alpha-naphthylthiourea (ANTU) intoxications, organophosphate compounds, chlorine, carbon monoxide, ammonia, or hydrogen sulfide. Decreasing oxygenation capacity is another mechanism that can be produced by hemolysis in poisoning with saponin-containing plants or by methemoglobinemia or carboxyhemoglobinemia in nitrite/nitrate intoxication and carbon monoxide intoxication, respectively. The last mechanism consists in altering the oxidative tissue metabolism by inhibiting oxidative systems (cytochromes, cytochromoxidase) that may occur in cyanide, hydrogen sulfide, opaque, or fluorine intoxications [14].

As for the diagnosis of acute toxic respiratory insufficiency, in the initial phase, the signs and symptoms of background intoxication are highlighted. Once the respiratory failure has occurred, its symptoms, which are generally circumscribed to the pathophysiological mechanisms involved, become evident. In acute respiratory failure (ARF) from CNS disorders, consciousness status can be abolished and respiratory movements diminished in amplitude and frequency. The symptoms of ARF by affecting the resilient muscles are dominated by generalized muscular asthenia and dyspnea, and in the ARF by pulmonary damage, the tachypnea is more common. The clinical signs associated with hypercapnia and hypoxia in comatose patients are psychomotor agitation, dyspnea, and cyanosis [4]. However, the severity of cyanosis does not adequately reflect the severity of respiratory insufficiency. Increased intracranial pressure due to cerebral vasodilatation may result in cerebral edema, causing headache, obtundation, and even coma.

Blood gas analysis may reveal respiratory acidosis (pH < 7.35 and $PaCO_2$ > 45 mmHg), which can be partially compensated by lowering the alkaline reserve and, in the absence of oxygen therapy, decreasing $PaCO_2$. A serious form of acute respiratory failure is acute respiratory distress syndrome (ARDS) manifested by bilateral pulmonary infiltration on radiography, PaO_2/FiO_2 ratio (partial oxygen pressure in arterial blood/oxygen fraction in the inspired air) below 200 mmHg and hemodynamic parameters within normal limits [12].

Corticosteroids and antibiotics may be used for the prophylactic purposes. Corticosteroids have been used for many toxic inhalational injuries. The prophylactic treatment of patients with inhalation injury with antibiotics has a empirical support [14, 15]. Essential therapy aims to ensure adequate blood oxygenation. Ensuring the ventilatory support should be seen in dynamics. Thus, ventilatory support begins with the least invasive supportive methods and progresses to the most aggressive techniques; you must minimize risks such as pneumothorax [16]. Oxygen supplementation is indicated for patients with suspected or confirmed respiratory failure.

Approximately 10% of children admitted to the PICU for poisoning may require endotracheal intubation [6]. After the decision for mechanical ventilation has been made, the route needs to be selected. Some experts prefer oral intubation because it allows the use of a larger endotracheal tube—usually 8 mm or more in adults—than nasal intubation [17]. A wide range of equipment is necessary to allow for a wide range of patient size. A selection of both straight and curved blades should be available. Capnography should be available to assist the endotracheal tube placement in the airway.

The goal of mechanical ventilation is to provide a sufficient exchange of oxygen and carbon dioxide and the metabolic needs of a patient to be accomplished with minimum adverse effects [4]. The purpose of mechanical ventilation is not always to achieve the normal blood gas concentration. Given the predisposition to hypoventilation and the risk of acute pulmonary edema, the mechanical ventilation of patients intoxicated with salicylates requires a lot of attention [18, 19]. High-frequency ventilation and ECMO should be considered to treat some severe intoxications, but there are limited reports on their use in pediatric toxicology [4, 20].

Noninvasive ventilation refers to providing the ventilation support without an invasive artificial path (intubation or tracheostomy probe). Patient selection is made taking into account noninvasive ventilation indications and contraindications as well as predictive factors of success or failure. Before starting noninvasive ventilation, a plan should be established to be applied if therapy fails. Noninvasive ventilation can be done with either portable CPAP or BiPAP devices that can also be used for home ventilation with either intensive ventilation or portable ventilation. One of the common causes of failure of noninvasive ventilation is the large air loss around to the ventilation mask [21].

4.2 Neurological complications

These are often the most prevalent symptoms in accidental or voluntary poisonings. Acute voluntary poisonings often involve psychotropic drugs (anxiolytic-hypnotic, antidepressant, antipsychotic, etc.) or ethanol, whose central toxic target is the central nervous system. If the alteration of consciousness is a frequent complication of poisoning, mortality directly attributable to neurological impairment is small compared to other etiologies (traumatic, vascular, etc.). Alteration of consciousness is most often due to a functional and reversible nature. It results from an interaction with one or more essential neurotransmitters (gamma-acidobutyric acid, serotonin, dopamine, etc.). However, lesional damage remains possible in case of exposure to a toxicant that prevents oxygen cellular use (e.g., carbon monoxide), when late detection or cardiopulmonary resuscitation complications cause anoxic or ischemic brain injury and ultimately neurovascular lesions [4, 22].

4.2.1 Acute alteration of consciousness

This is one of the most common pediatric emergencies. Its most serious form, coma, is one of the most critical situations faced by a doctor. Child coma occurs on an immature and fragile brain. In all cases of coma under the age of 7 years (including accidental poisoning), there is a risk that child's natural development achievements process will be compromised because the damage to the nervous system occurs during the full development process [23, 24]. The central nervous system (CNS), due to its rich lipid content and abundant vascularization is frequently the target organ for many toxic and nontoxic drugs. In intoxications, coma may occur due to direct toxic effects, metabolic abnormalities, or toxic-induced anoxia [25, 26].

The frequency of toxic coma varies in different studies, from 5% [26] to 28.9% [27]. In a recent prospective observational study, they accounted for 11.5% of all nontraumatic coma [28].

4.2.1.1 Anamnestic and clinical diagnosis of toxic comas

The toxic etiology of a coma must be raised in any patient who presents a severe deterioration of consciousness, without another obvious cause. In the absence of seizures, the patient often progresses to coma passing through the stages of

lethargy, confusion, and stupor. A carefully conducted anamnesis, taken from the caregivers, can sometimes indicate a poisoning. The child's age can provide important information. Small children are prone to accidental poisoning, and in this situation, questioning the caregivers about toxic substances found in the house may be useful. Adolescents tend to experience alcohol, psychoactive substances, or recreational drugs. In the absence of an obvious history, toxicological exams need to be conducted in serum and urine [29, 30].

The physical examination can also provide clues about a possible intoxication. Thus, a careful examination of the teguments may reveal signs of venous punctures suggesting a drug self-injection, including heroin. Sclero-tegumentary jaundice may be highlighted, suggesting a hepatic failure of a toxic cause that has evolved into a coma. Epistaxis may exist in snorting cocaine. The presence of head lesions should alert the doctor about the possibility of a possible simultaneous cranial trauma [31]. The vital signs are also important for orientation toward a toxic etiology. For example, benzodiazepines and opiates often cause respiratory depression. Amphetamines and cocaine can cause hypertension and tachyarrhythmias. Drugs that affect the autonomic nervous system may induce hyperthermia, vasoconstriction or vasodilatation, and heart rhythm disorders [32].

Neurological examination is very important for the diagnosis (**Figure 1**). Evaluation of the coma is important in unconscious patients (**Table 1**). The general characteristics of toxic coma are the absence of meningeal signs and neurological focal signs, unless hypoglycemia is involved. During neurological examination, the plantar, deep tendon reflex, and muscle tone must be examined. Depending on the changes found, one of the following three syndromes can be outlined: pyramidal, extrapyramidal, or myorelaxation, which may indicate the toxins involved in inducing coma.

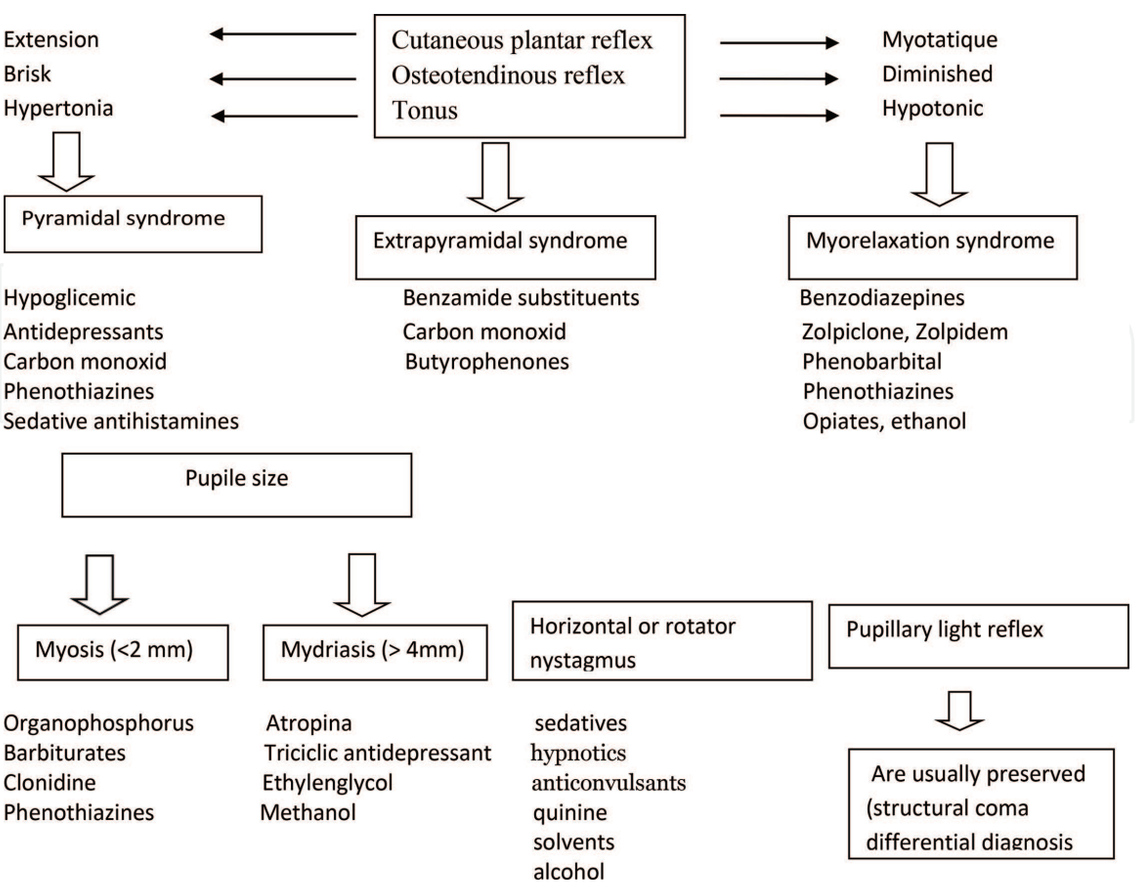

Figure 1.
Neurological examination of the patient with toxic coma [33].

Area assessed	Infant	Children	Score
Eyeopening	Open spontaneously	Open spontaneously	4
	Open in response to verbal stimuli	Open in response to verbal stimuli	3
	Open in response to pain only	Open in response to pain only	2
	No response	No response	1
Verbalresponse	Coos and babbles	Oriented, appropriate	5
	Verbal response	Confused	4
	Cries in response to pain	Inappropriate words	3
	Moans in response to pain	Incomprehensible words or nonspecific sounds	2
	No response	No response	1
Motor response	Moves spontaneously and purposefully	Obeys commands	6
	Withdraws to touch	Localizes painful stimulus	5
	Withdraws in response to pain	Withdraws in response to pain	4
	Responds to pain with decorticate posturing (abnormal flexion)	Responds to pain with decorticate posturing (abnormal flexion)	3
	Responds to pain with decerebrate posturing (abnormal extension)	Responds to pain with decerebrate posturing (abnormal extension)	2
	No response	No response	1

Table 1.
Modified Glasgow coma scale for infants and children.

Eye exams are essential for the toxic etiology. The type of coma associated with pupillary response may also suggest the toxin responsible for the coma appearance [33–35] (**Figure 1**). Periodic movement type "ping-pong" has been described in poisoning with monoamine oxidase inhibitors [34]. Hyperthermia is part of the anticholinergic syndrome; when associated with neurological disorders and toxic ingestion is not evident, then it is necessary to search for a *cerebromeningeal* infectious cause [31]. A convulsive coma may occur in the evolution of a poisoning with tricyclic antidepressants, phenothiazines, antihistamines, lithium, theophylline, carbamazepine, dextropropoxyphene, amphetamines, cocaine, and hypoglycemic substances [35]. Coma associated with hemodynamic disorders can be found in meprobamate poisoning, membrane stabilizers, calcium inhibitors, or beta-blockers [4]. Detecting some breathing disorders associated with coma may be suggestive of some toxics. Decreased respiratory rate below 12 breaths/min, with regular breathing, indicates opioids or sedative hypnotics. Some sympathomimetic agents (salicylates, amphetamines, CO) on the contrary stimulate breathing, causing tachypnea. Kussmaul-type breathing (high frequency, regular) is usually associated with metabolic acidosis from poisonings with ethylene glycol, methanol, or salicylates [36, 37].

4.2.1.2 Laboratory investigations

Useful investigations into a toxic coma are mainly in serum determinations and much less often in neuroimaging investigations. Any metabolic acidosis in a toxic coma requires further investigation. The presence of low anionic gap suggests lithium or bromine intoxication. Highlighting an osmolar gap usually indicates a poisoning with ethanol, isopropanol, methanol, or ethylene glycol. Pure respiratory acidosis is consistent with hypoventilation, possibly a sign of poisoning with

hypnotic sedatives or opioids. Although urinary toxicological tests may sometimes be useful in a toxic coma, the results are often false positive or false negative [24, 25].

Dosage of serum concentrations of some drugs is of great help, if available. Other useful investigations are the dosage of serum cholinesterases and carboxyhemoglobin. Coma caused by tricyclic antidepressants poisoning may be accompanied by electrocardiographic abnormalities (dysrhythmia) and seizures [38].

4.2.1.3 Treatment

The main life threat in toxic coma is the alteration of respiratory function. Therefore, maintaining airway permeability and ensuring effective breathing are a priority, because providing the O_2 requirement of the brain is essential. In any suspicion of hypoxia or CO intoxication, O_2 should be administered [32]. Not every child in a toxic coma should be intubated. It is estimated that orotracheal intubation is required in about 20% of toxic coma. The main indications are coma with alteration of swallow reflexes, acute respiratory failure unresponsive to O_2 administration, severe circulatory insufficiency or toxic comas associated with severe symptoms, refractory to pharmacological treatment (convulsions, hyperthermia) [33].

Glycemia should be measured as a matter of urgency, and if there is hypoglycemia, this must be quickly rectified. Activated charcoal gastrointestinal decontamination can sometimes provide benefits, if done early. Gastric lavage can be performed if the patient has the respiratory tract protected by endotracheal tube. If the toxic is adsorbed on the activated charcoal, it can be administered by nasogastric tube. There is a lot of attention needed when administered to non-intubated patients. Hemodynamic instability induced by toxic shock, which may be hypovolemic, distributive, or cardiogenic, requires vascular filling with saline or Ringer's solution, injected quickly and possibly vasopressor medication. Any detected heart rhythm disorders and hypertension or hypotension need to be corrected. Simultaneously with the stabilization measures, the antidote will be administered according to the protocols in toxic-induced coma [25].

In comas of unknown etiology, the concept of "coma cocktail" containing dextrose, oxygen, naloxone, and thiamine (vitamin B1) was proposed. But indications and efficiency were controversial.

Currently, in toxic comas, precise indications for flumazenil and naloxone are used. Flumazenil acts by a competitive mechanism at the benzodiazepine receptor level, canceling the sedation effects of benzodiazepines within 1–2 min of administration. In the case of children, we start with a dose of 0.01 mg/kg intravenously, which can be repeated 1–2 min to a total dose of 0.05 mg/kg maximum 1 mg. It is effective in toxic-induced coma by zolpidem and zopiclone. If in a calm coma of undetermined etiology, there is no patient awakening after the administration of flumazenil referred to dose, the diagnosis of intoxication with benzodiazepines is infirmed [39]. Naloxone is a pure opioid antagonist, which acts by competitive antagonism at μ receptors to determine the reversibility of respiratory depression, hypotension, and miotic within 2 min. For children >3 years, the indicated dose is 0.01–0.1 mg/kg. If the desired effect is obtained, it may be repeated two times at an interval of 5 min; the dose may reach 10 mg. Regardless of the way of administration (intravenous, subcutaneous, intramuscular, endotracheal intubation probe, or inhalation), the effect is similar. The lack of response within 15 min after administration requires looking for another coma cause [4, 5].

Extrarenal epuration may sometimes have indications in coma due to alcohol intoxications (ethylene glycol, isopropyl alcohol, and methanol), salicylates, theophylline, lithium, valproic acid, carbamazepine, or carbamates [40].

4.2.1.4 Prognosis

The prognosis of toxic coma is generally better than that of anoxic coma. For example, in sedative poisoning, mortality is below 1%. The following neurological signs provide a poor prognosis for recovery from toxic coma: absence of corneal reflexes after day 1, absence of eye opening response on day 3, loss of pupillary reflexes (up to 1 week), lack of oculovestibular response, abnormal skeletal muscle tonus, the absence of spontaneous eye movement, the isoelectric pathway on the electroencephalogram [25].

Some toxic may cause prolonged coma (>100 h) with intermittent agitation periods known as cyclic coma: barbiturates, carbamazepine, clonazepam, ethchlorvynol, glutethimide, meprobamate, olanzapine, quetiapine. Short-term memory alteration and postcoma amnesia are possible, secondary to neuron damage in the pyramidal system at the hippocampus level in CO intoxication [25, 38].

4.2.2. Convulsions

Convulsions are common in situations when the toxic involved affects the central nervous system. In the context of poisoning, seizures are often a sign of severity [41]. From the clinical point of view, toxic-induced convulsions can occur with or without warning signs (e.g., aura) or mental state alteration. Most toxic-induced seizures are generalized, tonic–clonic ("grand mal"). Epileptic status is defined as a continuous convulsive activity lasting more than 30 min or more convulsive episodes between which consciousness is not completely regained [4, 5, 42]. Patients with preexisting epileptogenic focal conditions may experience focal seizures [42].

4.2.2.1 Etiology of toxic seizures

Table 2 presents the etiology of toxic seizures.

4.2.2.2 Treatment of toxic seizures

Seizure control in PICU is a fundamental problem in the management of a poisoned child. Convulsions associated with toxic ingestion are sometimes difficult to control, being recurrent or persistent leading to status epileptics. This is associated with an increase in oxygen in the brain level. The imbalance between supply and demand can lead to cerebral ischemia. That is why an aggressive management of toxic seizures is critical to preventing brain damage. The first priority in managing seizure crises is to provide airway permeability and oxygen therapy to ensure delivery of oxygen to the brain. Evaluation and correction of electrolyte disturbances and hypoglycemia should also be promptly performed [4, 43]. The first therapeutic line for toxic-induced convulsions is represented by benzodiazepines (diazepam, lorazepam, or midazolam). Lorazepam and diazepam exhibit a similar clinical response time (until termination of seizure activity) [41, 42]. However, after treatment with lorazepam, the rate of seizure recurrence appears to be lower [44]. Also, according to some studies, lorazepam has been shown to have a longer duration of action of the anticonvulsant effect (12–24 h vs. 15–30 min) and is therefore the preferred choice of some clinicians [42]. The preferred route of administration of benzodiazepines is intravenous. **Table 3** lists the doses of benzodiazepines that can be used in toxic-induced convulsions in children and adolescents.

In the absence of response to benzodiazepines, phenobarbital or valproic acid may be effective for crises control. Phenytoin is less effective in the treatment of induced seizures [42]. If seizures do not stop at the referred medication, it is

Class	Example(s)	Class	Example(s)
Pharmaceuticals		**Nonpharmaceuticals**	
Analgesics	Meperidine/normeperidine, propoxyphene, pentazocine, salicylate, tramadol	Alcohols	Methanol, ethanol (withdrawal)
Anesthetics	Local anesthetics *(lidocaine, benzocaine)*	Antiseptic/ preservatives	Ethylene oxide, phenol
Anticonvulsants	Carbamazepine	Biologic toxins	
Antidepressants	Tricyclic (amitriptilina/ nortriptyline), amoxapine, bupropion, selective serotonin reuptake inhibitors (citalopram), venlafaxine	Marine animals, mushrooms, plants	Domoic acid [shellfish (blue mussels)], monomethylhydrazine (*Gyromitra* spp.), coniine (poison hemlock), virol A (water hemlock), camphor
Antihistamines	Diphenhydramine, doxylamine, tripelennamine	Gases (naturally and/or anthropogenically occurring)	Carbon monoxide, hydrogen sulfide, cyanide
Antimicrobials	Antibacterials (selected penicillins, cephalosporins, carbapenems, fluoroquinolones), antimalarials (chloroquine), tuberculostatics (isoniazid)	Metals/ organometallics	Alkyl mercurials (dimethylmercury), arsenic, lead, thallium, tetraethyl lead, organotins (trimethyltin)
Antineoplastics	Alkylating agents (busulfan, chlorambucil)	Metal hydrides	Pentaborane, phosphine
Antipsychotics	Clozapine, loxapine	Pesticides	
Antiasthmatic	Theophylline	Fungicides/ herbicides	Dinitrophenol, diquat, glufosinate
Cardiovascular drug	Propranolol, quinidine	Insecticides	Organochlorines (DDT, lindane), organophosphates (parathion), pyrethroids (type II), sulfuryl fluoride, alkylhalides (methyl bromide)
Cholinergics	Pilocarpine, bethanechol	Molluscicides	Metaldehyde
Muscle relaxants	Baclofen, orphenadrine	Rodenticides	Strychnine, zinc, or aluminum phosphide
Nonsteroidal anti-inflammatory drug	Mefenamic acid, phenylbutazone		
Psychostimulant/ anorectics	Amphetamine, caffeine, cocaine, methamphetamine, 3,4-methylenedioxymethamphetamine, synthetic cannabinoids		
Vitamins/ supplements	Vitamin A, ferrous sulfate		

Table 2.
Proconvulsant agents (adapted after Hanson [44]).

necessary to induce coma with sodium thiopental or propofol. To induce a coma, sodium thiopental is administered as a bolus of 3 mg/kg, which is repeated after 2 min, followed by maintenance with 1–15 mg/kg/h. For propofol, the dose is 1–5 mg/kg bolus (repeatable) followed by continuous infusion up to a maximum

Benzodiazepine	Pediatric dose
Lorazepam	0.05–0.1 mg/kg iv (maximum 4 mg/dose). It can be repeated at 10–15 min if necessary. Maximum dose: 8 mg/12 h
Diazepam	<5 years: 0.2–0.5 mg/kg iv every 2–5 min up to a maximum total dose of 5 mg. >5 years: 1–2 mg iv every 2–5 min up to a maximum total dose of 10 mg.
Midazolam	>2 months: 0.15 mg/kg iv bolus, followed by a continuous infusion of 1 μg/kg/min, titrating the dose every 5 min until seizure control. Mean dose: 2–3 μg/kg/min.

Table 3.
Posology of benzodiazepines in seizures in childhood (adapted after Blais and Dubé [41]).

of 5 mg/kg/h [45]. A special category of seizure, which does not respond to traditional therapy, is that of isoniazid intoxication. In this case, the crises result from exhaustion of pyridoxine (vitamin B6) and respond only to its administration [4]. In case of intoxication with isoniazid, the vitamin B6 posology is 1 gram per gram of ingested isoniazid (maximum 5 grams). This dose will be given slowly within 10 min, or until seizures cease. If the seizures stop during administration, the remaining dose will be given within the next 4 h. If the dose of isoniazid is unknown, 70 mg/kg iv (maximum 5 g) should be administered in the same manner. The initial dose may be repeated once seizures relapse. Pyridoxine is also anticonvulsant therapy of choice in intoxication with gyromitra mushrooms in the dose of 25 mg/kg iv in 10 min and can be repeated in case of seizure recurrence [41].

4.3 Cardiovascular disorders

These are a serious complication of some poisoning, requiring prompt monitoring and treatment. Assessing a poisoned child at risk of cardiovascular disease requires a detailed physical exam. In addition to cardiac volume and output evaluation, a series of laboratory tests must be performed: blood gases, electrolyte dosing, blood sugar, transaminases, and azote retention tests. In some cases, the serum level of the toxic substance can also be determined, which helps to assess the severity of intoxication and to support the therapeutic decision. Additional care management such as blood pressure measurement, electrocardiography, and echocardiography can also be useful to guide therapy in case of a poisoning accompanied by cardiovascular instability. Identification of a certain toxic can simplify the treatment through specific intervention. If the poison is unknown, the initial resuscitation consists in administration of intravenous fluids to maintain a proper intravascular volume [4, 5]. Rapid administration of 20 ml/kg bolus isotonic fluids, usually crystalloid (normal saline or Ringer's lactate) over 10–15 min, is used to restore intravascular volume. Additional fluid bolus may be required depending on the reassessment of intravascular volume [46]. However, the intravascular volume should be corrected cautiously, because too vigorous expansion may lead to fluid retention, liver enlargement, signs of pulmonary edema, jugular vein distension, or cardiomegaly, without improvement of vital signs and tissue perfusion. Positively inotropic agents are required in such patients. The cardiovascular disorders, which are present at the time, determine which inotropic agents and vasopressor drugs to choose.

Arrhythmia is a frequent complication in cardiovascular drug poisoning. Dysrhythmia may occur by direct affecting of the electrical conduction system of the heart, by changing the electrical membrane potential across the myocardial cell, or by indirect disturbance of the electrical conduction system through the nervous system or due to electrolytic and metabolic disorders, which affect the electrical activity of the heart.

4.3.1 Bradyarrhythmias: etiology and treatment

Bradyarrhythmias occur due to some toxic substances, which decrease the central nervous system influx or the chronotropic activity of the conduction system. Agents that can induce bradyarrhythmias are tricyclic antidepressants, α2-adrenergic agonists, β-adrenergic blockers, calcium channel blockers, cholinomimetics, digoxin, sedative hypnotics, organophosphorus and carbamates, plants containing cardiac glycosides, opioids, cocaine, organophosphorus, and carbamates [47].

Bradyarrhythmia due to ingestion of unknown toxic substance is managed with supportive treatment. Atropine or positive inotropic agents, such as epinephrine, are used to correct bradyarrhythmia. When the toxic agent is known, the aim of the therapy is to antagonize the toxic effects (e.g., calcium chloride is used to treat calcium channel blockers intoxication). Literature data showed that in poisoning with β-blocker, calcium channel blocker, and tricyclic antidepressant, glucagon may be used, given its positive inotropic and chronotropic effects. Glucagon dose in children is 0.03–0.15 mg/kg in 1–2 min bolus, followed by 0.07 mg/kg/h infusion or by repeated boluses in 5–10 min, as needed [48]. Other therapies that may be used in severe β-blocker and calcium channel blocker poisoning are hyperinsulinemia—euglycemia (HIE) and intravenous fat emulsion (IFE) [49]. In bradycardia mediated by vagal reflex, atropine is the treatment of choice. For unresponsive sinus bradycardia, as well as for junctional or ventricular bradyarrhythmias, isoproterenol may be used. Specific therapy should also be used (calcium in calcium channel blockers intoxication; digoxin antibodies in digoxin poisoning). Sodium bicarbonate is beneficial in tricyclic antidepressant poisoning. Concomitant correction of electrolyte disturbances, hypoxia, and acidosis is mandatory because they may contribute to failure of pacing stimulus to depolarize cardiac cells [47]. In severe cases of bradyarrhythmia or heart block unresponsive to pharmacological therapy, direct transthoracic pacing may be necessary.

4.3.2 Tachyarrhythmias

Tachyarrhythmias are common in poisonings. They are classified as wide-complex and narrow-complex rhythm (**Tables 4** and **5**).

Electrocardiogram (ECG) in narrow-complex tachyarrhythmias shows sinus tachycardia or supraventricular tachycardia (normal conduction).

Specific therapies include antidotes depending on xenobiotic. Treatment imposes corrections of hypotension, hypoxia, or electrolyte abnormalities and administration of esmolol or other short-acting beta-blocker for intractable tachycardia in the absence of hypotension or other signs of myocardial depression [4, 47].

ECG in wide-complex tachyarrhythmias may show ventricular tachycardia (VT) monomorphic or polymorphic, ventricular fibrillation (VF), ECG signs preceding

Anticholinergic: amantadine, antihistamines, atropine, belladonna, scopolamine, cyclic antidepressants, mushrooms (muscarine-containing, e.g., clitocybe dealbata), neuroleptics (thioridazines and mesoridazines also are membrane depressants), plants (e.g., Jimson weed)
Sympathomimetic: amphetamines and their congeners (e.g., ecstasy), caffeine, chloral hydrate, cocaine, ethanol, ephedrine and pseudoephedrine, lysergic acid diethylamide (LSD) and other hallucinogens, monoamine oxidase inhibitors, phencyclidine, scorpion or spider envenomation, sedative-hypnotic withdrawal, selective serotonin reuptake inhibitors, theophylline
Cholinomimetic: organophosphates

Table 4.
Poisoning-induced narrow-complex tachyarrhythmias.

Antiarrhythmics (type Ia, Ic, III), antihistamines, arsenic, cardiac glycosides, cyclic antidepressants, carbamazepine, chloral hydrate
Other toxic: sodium fluoride, freon (and other fluorocarbon aerosols), hydrocarbon solvents, neuroleptics, propoxyphene, quinine, and related agents

Table 5.
Poisoning-induced wide-complex tachyarrhythmias.

VF/VT, supraventricular tachyarrhythmias, prominent R wave lead AVR, rightward deviation of QRS axis, and QT prolongation [47].

Correction of possible hydroelectrolytic and acido-basic imbalance is required in treatment of toxic ventricular tachycardia. In monomorphic ventricular tachycardia, if the patient's condition is stable and there is no hemodynamic instability, chemical cardioversion with amiodarone 5 mg/kg iv, or procainamide 15 mg/kg iv or lidocaine 1 mg/kg bolus is first attempted. In wide QRS complex tachycardias, adenosine is not useful. If the chemical cardioversion has results, the drug will be administered by continuous intravenous infusion to avoid relapses. The IV infusion time will be decided along with the pediatric cardiologist. If the chemical cardioversion is ineffective, synchronized biphasic electrical cardioversion with 0.5–1 J/kg is needed [47, 50]. In polymorphic ventricular tachycardia with hemodynamic instability, the treatment is based on electrical cardioversion associated with magnesium. If magnesium sulfate is ineffective or bradyarrhythmias occur, isoproterenol IV may be useful. Hypokalemia can exacerbate ventricular tachycardia, and therefore, potassium supplementation is required even in patients with normal potassium at the time of determination.

Bidirectional ventricular tachycardia is a hallmark of severe digitalis toxicity, and immediate specific antidote treatment with FAB antibodies must be started. This type of ventricular tachycardia may occur in aconite poisoning too [51, 52].

Torsades de pointes (TdP) is a specific type of polymorphic ventricular tachycardia exhibiting a characteristic morphology on the electrocardiogram, in which the QRS complexes "twist" around the isoelectric line. This is a major toxin-induced arrhythmia, which may degenerate into ventricular fibrillation and sudden death [53, 54]. In this situation, the corrections of electrolyte disorders, bradycardia, acidosis, low blood pressure, and hypoxia are needed. If poisoning involves a drug with Na^+ channel blocking properties (e.g., tricyclic antiarrhythmic drugs, cocaine, class IA and IC antiarrhythmic drugs, or antipsychotic drugs), sodium bicarbonate may be used to reduce the degree of sodium channel blockade by increasing extracellular sodium [55]. The treatment of choice in torsade de pointes is magnesium sulfate. The pediatric dose is 25–50 mg/kg iv. If a poisoned patient does not respond to the abovementioned therapeutic measures, intravenous lipid emulsion therapy should be considered if the drug has lipophilic properties. A last therapeutic alternative is arteriovenous extracorporeal membrane oxygenation (ECMO) [47, 55].

5. Techniques for extrarenal treatment in toxicology

The Extracorporeal Treatments in Poisoning (EXTRIP) Workgroup is a group of international experts spanning disciplines of nephrology, toxicology, pediatrics, emergency medicine, critical care, and clinical pharmacologists that has been reviewing the evidence in the literature and provide recommendations for the use of extracorporeal treatments in poisonings. To date, EXTRIP has published systematic reviews on the role of extracorporeal treatment (ECTR) for poisoning from acetaminophen, barbiturates, carbamazepine, digoxin, lithium, metformin, methanol, salicylates, thallium, theophylline, tricyclic antidepressants, and valproic acid [56]. Waste treatment methods are

numerous, and techniques and/or equipment continuously evolve. It mainly involves hemodialysis, hemoperfusion, hemofiltration, and albumin dialysis [57].

5.1 Hemodialysis

Hemodialysis is the technique of removing toxins from the blood using a diffusion gradient through a semipermeable membrane. To be dialyzable, poisons must meet the following conditions: hydrosolubility, low molecular weight, apparent low volume of distribution, low protein binding, and low endogenous clearance [5]. It may be necessary in the following situations: severe poisoning with salicylates, accompanied by important mental disorders, in some phenobarbital intoxications, ethylene glycol, lithium, and theophylline [4, 6].

Possible complications of hemodialysis are hypotension, hypoxemia, bleeding, embolism, and cardiac rhythm disorders [4].

5.2 Hemoperfusion

The hemoperfusion column can be considered as an extracorporeal clearance organ, increasing the overall clearance of the body. Its efficacy is superior to hemodialysis or hemofiltration. It has been proposed in serious poisonings with theophylline, carbamazepine, and cardiotoxic (membrane stabilizers, inhibitors calculation, and meprobamate) that do not quickly respond well to symptomatic treatment led. Its indication should be taken into account very early and in intoxications with some toxic lesions such as colchicine or paraquat [57]. Complications of hemoperfusion can be thrombocytopenia (30%), leukopenia (10%), hypocalcemia, hypoglycemia, reduction of fibrinogen, and hypothermia. The future lies in hemoperfusion devices coated with drug-specific antibodies or the antidote of the toxin instead of activated charcoal [58].

5.3 Hemofiltration and hemodiafiltration

Hemofiltration and hemodiafiltration have similar properties as hemodialysis regarding the distribution volume and protein-binding percentage. Water-like substances move out of the plasma through the membrane, and this fluid is replaced with isotonic fluids. The rate of removal of the toxin is influenced by the degree of protein binding and the ultrafiltration (UF) and the sieving coefficient, which is the ability of the solute to cross a membrane by convection. Although this makes high-efficiency convective techniques suitable for poisoning, reports of their use in poisoned patients remain limited due to their higher technical requirements and lesser availability [58, 59].

5.4 Other purification techniques used in toxicology

The most developed and most commonly used hepatic dialysis systems are the molecular adsorbent recirculation (MARS) and fractional plasma separation and absorption (Prometheus).

5.4.1 MARS albumin dialysis

MARS is a hemodialysis technique that combines the selective removal of albumin-bound toxins with the removal of water-soluble toxins. The MARS system uses a 20% human albumin solution as a dialyzate and a semipermeable membrane as a dialyzer.

The albumin acquires an increased ability to bind toxins through contact with membrane's polymers. Through the membrane, the patient's blood comes into

contact with the albumin solution, and the albumin-related toxins cross the membrane and enter the dialyzate, the transfer being made in the sense of the existing concentration gradient between the blood compartment and the albumin solution. After detoxification, the albumin solution is recirculated, coming into contact with the patient's blood again [60–62]. Several small randomized controlled trials and case control studies in adults showed significant improvement, both in morbidity and mortality, in patients treated with MARS. However, there are little data on the use of MARS in the children [63].

5.4.2 The Prometheus system

It consists of a bloodstream where two filters perform a purification of water-soluble toxins and then a fractional separation of plasma, so that cellular components and macromolecules are separated by albumin and by low-molecular-weight solvents. Then, the autologous albumin solution crosses a neutral resin filter, which has an increased affinity for bile acids, aromatic amino acids, and phenols, and also an anion exchange resin filter that removes unconjugated bilirubin [64–66].

These techniques were initially used in hepatology. Subsequently, they were also used for the treatment of acute poisonings with or without liver failure, especially the MARS technique. The aim is to remove albumin-related toxic substances. There are several reports regarding the use of these purification techniques in high liver toxicity mushrooms poisoning as *Amanita phalloides* [60, 62, 64] and also in paracetamol poisoning [56, 60]. These techniques were also used to treat phenytoin, theophylline, and diltiazem poisoning, and for calcium channel blockers poisoning too [57, 67].

5.4.3 Arteriovenous extracorporeal membrane oxygenation (ECMO)

ECMO is a special technique for maintaining pulmonary and cardiac function through an extracorporeal circulation pump. The purpose of this method is to provide a good oxygenation support and remove the excess of CO_2. It is an exceptional therapy proposed for serious poisonings, especially those that are complicated with respiratory distress syndrome or cardiogenic shock refractor on conventional therapy [68]. ECMO is difficult and should only be done in experienced centers as it carries significant risks. It is a method that requires systemic anticoagulation. The main possible complications are bleeding, systemic infection, and thromboembolic accidents [4, 68]. If the ECMO indication has been established, this therapy should be initiated as soon as possible, before irreversible cerebral or visceral anoxic lesions [68, 69].

6. Organ donation

Despite the best efforts of the care team, it is not possible to save every child with poisoning. Particularly, in cases where there was significant hypoxic–ischemic central nervous system injury, patient may progress to brain death [70]. Because poisoning is not a sign of organ donation, these patients can be a potential donor source [71]. Toxicological risk assessment should be rigorously conducted in the sense that the transmission of intoxication to the recipient should be avoided. Some toxic substances accumulate in the liver, heart, or lung and could theoretically be released from these grafts after transplantation. These risks, however, should not be exaggerated. They can be diminished by knowledge of kinetics and toxics in target organs. Taking risks is more important for heart or kidney transplantation, organs

that are more susceptible to anoxic-ischemic damage [4–6]. Since severe depression of the central nervous system induced by some toxic can mimic brain death, it is important to allow sufficient time, depending on the pharmacology of the toxic substance, until the plasma concentration decreases to an acceptable level. To declare cerebral death, the following are necessary [4, 72, 73]:

- clinical criteria: deep, dormant coma, absence of brain stem reflexes, absence of spontaneous breathing;
- biological criteria:
  - mandatory: flat track on the EEG, apnea test, atropine test;
  - optional: cerebral angiography (stroke), transcranial echo-Doppler, scintigraphy, etc.

The conditions for declaring brain death vary according to the country's legislation. Basically, the patient's examination should be performed by two physicians: neurologist or neurosurgeon and anesthetist. In children, the intervals between examinations must be 24 h for the child aged 2 months to 1 year and at least 12 h over 1 year [74].

7. Conclusion

Complications of poisonings during childhood may enforce hospitalization to PICU and may contribute to lowering the survival rate. Supporting vital functions is the main objective of the management of a poisoned patient admitted in PICU.

Conflict of interest

None.

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