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Cardiogenic shock in acute cardiotropic poisoning in children. Epidemiology. Diagnosis. Emergency treatment

PHD THESIS SUMMARY

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CONTENT

INTRODUCTION

Exposure of the pediatric population to toxic agents is a major public health problem, with children being particularly vulnerable to the adverse consequences of poisonings. The characteristic behaviour of young children to explore the environment makes them ingest toxic substances with unpleasant tastes or odours, which can be avoided by older children or adults (1,2). Very young children are underweight, have limited physiological reserves and poorly developed metabolic pathways, making them more susceptible to post-exposure lesions, even to small amounts of toxic. By comparison, adolescents have an increased tendency toward intentional poisoning, typically more severe than unintentional exposure (3,4).

The term shock in critically ill patients, including poisoned patients, is defined by a significant decrease in systemic tissue perfusion, leading to an inadequate amount of oxygen and nutrients supplied to the vital metabolic needs of the organs. This discrepancy between oxygen intake and consumption leads to cellular hypoxia, which disrupts biochemical processes at the cellular level and can progress to a systemic reaction. Ionic pump dysfunction, impaired membrane permeability, intracellular oedema, and cellular acid-base imbalances result in altered serum pH and endothelial dysfunction, triggering the inflammatory and anti-inflammatory cascade. Progressive cell destruction followed by organ damage and multiple organ failure may eventually lead to death (5,6).

The risk of death involves a combination of factors such as the underlying aetiology, the association of chronic conditions, the host's immune response, and the timeliness of appropriate diagnosis and therapy (7). The prognosis of patients with cardiogenic shock depends on early recognition and proper treatment. Fulfilling these goals has led to a continuing decline in pediatric mortality, but the shock associated with insufficient multiple organs (MSOF) remains one of the leading causes of death.

Toxicological research is often limited to clinical case reports, small series of cases or animal studies; therefore, most treatment recommendations and guidelines are based on expert consensus or personal experience rather than evidence-based medicine. While the criteria for hypotension and shock diagnosis and treatment in adults or pediatric septic patients are recent, well-documented, and result from multicenter studies, protocols for circulatory disorders due to acute poisoning are quite poor and little evidence-based (8–10). Thus, due to the low incidence of these severe poisonings, especially among children, the chances of conducting a

randomized controlled trial to demonstrate the effectiveness of these protocols are difficult to implement (11).

Most hemodynamic data in critically ill patients are obtained from non-toxicological cases, so it is often unclear whether they can be extrapolated to poisoned patients (12).

Following an extensive bibliographic study, I noticed a shortage of scientific articles in the literature to analyze well-represented groups of pediatric patients. Based on these premises, I considered it necessary to conduct a more detailed study on epidemiology, therapy and the evolution of cases of severe acute intoxication (13–16).

The motivation of the study was also supported by the increase in the number of severe acute poisonings, especially with cardiotoxic agents, a conclusion presented in several scientific papers in the field of pediatric toxicology (17–19).

This doctoral thesis aims to perform a detailed analysis of the severe acute poisoning with cardiotoxic substances complicated by cardiogenic shock of the patients admitted to the Toxicology - Intensive Care Department from the "Grigore Alexandrescu" Children's Emergency Hospital for seven years.

The doctoral thesis consists of a generic section that presents the current notions that characterize pediatric acute poisoning complicated by cardiogenic shock and a specific section that includes a personal contribution to the evaluation and approach of this pathology.

The personal research is structured in four parts: two statistical studies, a selection of patients with particular evolution presented in extenso and the development of some emergency algorithms for approaching the acute poisonings with cardiotoxic substances.

The first research study aims at a detailed analysis of the epidemiological characteristics, aetiology and therapeutic methods used, to subsequently correlate the patient's clinical and biological picture and his evolution.

CHAPTER 1. SHOCK

1.1. Definition of shock

Shock is a complex clinical syndrome characterized by an acute dysfunction of the circulatory system, resulting in the disruption of the supply and demand of oxygen. Insufficient oxygen in the tissues cannot support normal aerobic cellular metabolism and diverts it to anaerobic metabolism, which is much less efficient (5,20). The circulatory system thus does not fulfil its primary function of providing the cellular energy substrate and the elimination of metabolic products (20).

1.2. Pathophysiology of shock

The mechanisms of hypotension and shock from acute poisonings are multiple and can combine cardiac, central or peripheral mechanisms. Maintaining systemic tissue perfusion and blood pressure correlates with adequate cardiac output and systemic vascular resistance (SVR). Cardiac output may be decreased by toxic-induced myocardial damage, arrhythmias (impulse formation disorders, conduction or rhythm disturbances), a relative decrease in venous vasodilation, or absolute hypovolemia (actual fluid loss or third compartment) (5,6).

1.3. Cardiovascular toxicity

Cardiovascular damage associated with acute poisoning is a severe complication that requires prompt intervention and complex specific management. A thorough understanding of the imbalances produced by each toxicant, along with complex cardiovascular assessment, supportive treatment, and monitoring techniques, is essential for the effectiveness of critical patient treatment (39).

1.4 Epidemiology

Many substances produce cardiovascular side effects associated with drugs through various mechanisms of action depending on the causative agent. The most common include arrhythmias (ventricular tachycardia, ventricular fibrillation, torsade de pointes), hypotension or circulatory failure, myocardial injury (assessed by cardiac enzymes and ECG) or heart attack (47). Although precise epidemiological data are brief, they indicate that an increased morbidity and mortality rate follow cardiovascular complications in acute poisoning.

CHAPTER 2. CARDIOGENIC SHOCK DIAGNOSIS

Shock is a clinical diagnosis based on a thorough history and examination. Any patient suspected of acute cardiotropic poisoning should be evaluated immediately for possible haemodynamic impairment. Minimum assessment measures require continuous cardiac monitoring, including pulse oximetry, noninvasive blood pressure measurement, and a 12-lead electrocardiogram to identify cardiac ischemia, arrhythmias, and possibly QRS complex enlargement or QT prolongation (50).

2.1. History of the patient with acute poisoning

Obtaining a detailed history is the essential step in diagnosing a toxicological case. Therefore, it is imperative to collect data from all possible sources. Family, friends, and reporters often provide important diagnostic clues. Also, in today's highly digitalized society, the online space has become a new source of recruiting patient data, from text messages, emails or social media posts. These are all the more important as they are dated (30).

2.2. Physical examination of the patient with cardiogenic shock

The correlation between the patient's history and examination may confirm the initial suspected toxicological diagnosis. This may be the only source for differential diagnosis without any patient data. As such, there is no substitute for a thorough clinical examination by a direct toxicologist at the patient's bedside. They have the necessary experience to recognize certain specific signs of intoxication or toxidromes. Undoubtedly, the examination must be adapted to the particular circumstances and the clinical picture (16).

2.3. Toxidromes

After exposure to an unknown substance, the diagnosis of certainty can very rarely be made on isolated laboratory signs, symptoms or changes. The rapid and correct toxicological diagnosis is based on recognizing a pattern, corroborated by the presence or absence of suggestive clinical signs and detailed history.

2.4. Paraclinical evaluation

In addition to assessing circulatory status, laboratory changes should also be addressed to rapidly correct metabolic imbalances: acid-base balance with arterial gases, electrolyte dosage including calcium, magnesium and glucose, and basal liver and kidney function. Recognition of the toxicity to which the patient has been exposed, followed by dosing of its serum level, allows the assessment of the intoxication's severity and adaptation of treatment according to the anticipated evolution. In cases of acute poisoning in which cardiovascular instability is suspected, electrocardiography and echocardiography are recommended, the aspects of which may guide therapy (69).

2.5. Imaging evaluation

Diagnostic imaging is of limited value in the case of acute poisoning. There are exceptions, which can bring information in the ingestion of metals such as iron and lead. For example, X-raying of iron tablets indicates the prompt onset of gastric lavage.

CHAPTER 3. TREATMENT OF CARDIOGENIC SHOCK

3.1. General principles for approaching the patient with cardiogenic shock

The pediatric critically ill patient should be cared for in a pediatric intensive care unit, where there are specially trained medical staff and equipment appropriate to the needs of the children. If a severely poisoned patient is in a hospital with no possibility of adapted specialized care, all formalities should be done to reach a regional toxicology centre where a toxicologist can evaluate them. The transport of these critically ill patients must also be carried out by ambulances equipped with appropriate pediatric equipment, enabling emergency intervention, even during transport (93).

3.2. Initiation of therapy

Prompt and appropriate hemodynamic support to patients in shock is essential to prevent dysfunction and subsequent organ failure. The initial management of the shock must be problem-oriented. Therefore the initial response measures are the same regardless of the cause, although later, the final treatment to achieve the objectives may differ (96).

3.2.1. Volume resuscitation

Fluid requirements are usually determined by clinical criteria, such as heart rate, blood pressure, peripheral perfusion, and diuresis. However, these clinical indicators of organ perfusion do not precisely correlate with cardiac output (103). The assessment can be much more accurate by invasively monitoring central blood pressure and venous pressure as well as biochemical parameters for assessing overall perfusion, such as ScvO2, serum lactate, and base deficiency.

3.2.3. Classical vasopressors and inotropic substances

The combination of agents with positive inotropic and vasoactive effects must be adapted to the pathophysiology of each patient and must be accompanied by careful and permanent monitoring of cardiovascular status (110).

3.2.4. Other inotropic agents and inhibitors of phosphodiesterase III

Evidence from studies on the usefulness of new inotropic agents in the treatment of severe hypotension or shock is weak, as there is limited data in the literature regarding the use of inotropic substances in acute poisoning.

3.2.5. Levosimendan

Levosimendan (LSMD) acts through a single, dual mechanism. On the one hand, it is a calcium sensitizer, thus increasing the sensitivity of myocytes to calcium and, therefore, the contraction force being responsible for the positive inotropic effect. On the other hand, it opens ATP-dependent potassium channels in myocytes and vascular smooth muscle, thus being an arterial and venous vasodilator, a coronadilator and an anti-ischemic. In addition, LSMD also has phosphodiesterase inhibitory effects, similar to milrinone, but this effect occurs only at over-therapeutic doses (119).

3.2.6. Vasopressin analogues

Vasopressin analogues such as arginine-vasopressin and terlipressin are increasingly used off-label and may be effective in raising mean blood pressure, thereby reducing the need for catecholamines, although there is insufficient evidence to improve survival.

3.2.7. Intravenous lipid emulsion

Intravenous lipid emulsion (EIL) therapy has been shown to be beneficial and life-saving in systemic toxicity with local anaesthetics (TSAL).

3.2.8. Insulin in large doses

There is growing evidence that high-dose insulin therapy (1-10 units/kg/h), which is classically recommended for beta-blockers and calcium channel blockers, may be effective beyond certain isolated cases. Cases of favourable progression in amitriptyline, citalopram and amiodarone poisoning have been reported as an alternative to the failure of conventional therapies (136).

3.2.9. Methyl blue

Traditionally, methyl blue has been used as an antidote to methemoglobinemia, either hereditary or toxic. Recently, however, the issue of its adjuvant role in severe hypotension or shock, secondary to intoxication, anaphylaxis or sepsis, has been raised (137).

3.3. Prolonged external chest compressions with mechanical resuscitation devices

When severe hemodynamic disorders such as lack of cardiac output, heart attack, or ventricular fibrillation occur in acute intoxication, successful resuscitation requires effective chest compressions and/or defibrillation.

3.4. Extracorporeal life support

There are severe acute poisoning cases with cardiotoxic agents that are particularly associated with hypotension, shock or even cardiac arrest and do not respond to optimal conventional treatment. Some of these patients may require special therapies such as extracorporeal life support (ECLS) (81).

3.5. Continuation of emergency treatment

After the first hour of emergency therapy for shock reversibility, treatment aims to correct the associated organic dysfunction and should be performed in an intensive care unit.

PERSONAL CONTRIBUTIONS

CHAPTER 4. STATISTICAL ANALYSIS OF ACUTE POISONING COMPLICATED BY CARDIOGENIC SHOCK DURING 2014 - 2020

4.1. Introduction. Purpose. Objective

Cardiovascular toxicity refers to the side effects of extrinsic or intrinsic disorders of the heart or vascular system. Extrinsic ones involve exposure to drugs, natural and toxic products from the environment, while intrinsic ones involve exposure to toxic metabolites derived from non-toxic products such as those in food additives or supplements (29).

The spectrum of toxic cardiovascular manifestations can vary, ranging from vital signs and cardiac electrical activity abnormalities to signs of congestive heart failure and shock (17). All of these disorders may be present from the beginning of the presentation of his patient may be evolving.

Cardiogenic and/or vasoplegic shock is a rare complication in children with acute poisoning but is particularly severe and associated with a high mortality rate. In a two-year study of 151 patients with cardiovascular disease in the Toxicology Department of the SCUC, the prevalence of shock was 8.6%, and mortality among them was 38.5% (18).

The observational and retrospective research study aims to perform a detailed analysis of severe acute poisoning with cardiotoxic substances complicated by cardiogenic shock of patients admitted to the Toxicology - Intensive Care Department from "Grigore Alexandrescu" Children's Emergency Hospital, during seven years, in terms of epidemiology, diagnosis and the therapeutic methods used.

In this doctoral thesis that analyzes cases of severe acute poisoning complicated by cardiogenic shock in children, I set the following objectives:

• Evaluation of the demographic, etiological and circumstantial characteristics of the cases registered in the study

• Identifying correlations between the clinical and biological picture and the evolution of the pediatric patients

• Quantifying the timeliness of medical care and the impact on the patient's prognosis

• Analysis of the evolution and mortality of patients according to the therapeutic measures applied.

4.2. Material and method

4.2.1. Study type and batch characteristics

The personal study presented in this thesis is an observational and retrospective one, carried out over seven years, January 2014 - December 2020, in the Department of Toxicology - Intensive Care of the "Grigore Alexandrescu" Children's Emergency Hospital.

At the same time, the study is descriptive and inferential. On the one hand, the information collected was used to understand the available data (descriptive component) and, on the other hand, to discover new information about the events and the relationships between them (inferential component).

The group consisted of 1396 patients aged 0 to 18 years, admitted to the Department of Toxicology with severe acute cardiotropic poisoning diagnosis. From these was selected a statistically representative sample of 62 cases that associated at presentation or during hospitalization signs of cardiogenic shock.

Excluded from the study were known heart disease cases prior to toxic exposure and patients admitted for acute poisoning with cardiotropic and/or vasculotropic agents, who showed only impaired mental status due to the direct action of the toxicant without other manifestations associated with shock.

The criteria applied to establish the shock diagnosis were:

- weakly or absent pulse in the great arteries
- capillary recolouration time over 2 seconds
- hypotension
- cold, cyanotic, marbled extremities
- decrease in diuresis below 1 ml/kg/hour or anuria verified by sampling
- altered mental status.

4.2.2. Data collection

We analyzed the clinical observation papers of hospitalized patients diagnosed with severe acute poisoning with cardiotropic or vasculotropic substances and selected those who met the clinical criteria for shock. For the selected sample, we recorded in individual files their anamnestic, epidemiological, clinical - biological parameters, the therapeutic methods approached and the evolution.

4.2.3. Statistical data analysis

The collected data were processed using IBM SPSS v20 software. The results obtained were represented in percentages, frequencies, standard deviations, variants, means, and medians, depending on the situation.

4.2.4. Issues of medical ethics

The stages of compiling the studied group, the analysis of the clinical observation sheets and the taking over of the data necessary to perform the statistical analysis were carried out following the medical legislation in force.

4.3. Results and discussion

The personal study took place over seven years, from January 2014 until December 2020, in the Toxicology Department of the "Grigore Alexandrescu" Children's Emergency Hospital. During this period, in the hospital were registered 63078 cases, of which 7666 were diagnosed with acute poisoning. It has been researched the clinical observation sheets of

intoxicated patients, and among them, I identified those in which the etiologic agent was a cardiotropic substance, therefore with potential for evolution to cardiogenic shock, thus obtaining a batch of 1396 patients.

After a thorough analysis of the risk patients' evolution, I selected those who showed signs of cardiogenic shock at admission or in evolution, resulting in a sample test of 62 cases.

Each of the 62 patients included in the study group presented at least one of the cardiogenic shock diagnosis criteria (40,41):

4.3.1. Prevalence of cardiogenic shock in pediatric acute poisoning

During the seven years studied, 63078 hospitalizations were registered in the Pediatrics Department, with an average of 9010 cases per year. Of these, 7666 cases were admitted to the Department of Toxicology - Intensive Care, with an average of 1100 per year. It should be noted that the year 2020 was under the influence of the COVID 19 pandemic, so the number of hospitalizations was reduced by half. Among the hospitalizations with the diagnosis of acute poisoning during the seven years analyzed, 1396 had as aetiological agent a cardiotropic substance. The average of these patients with severe evolutionary potential, including cardiogenic shock, was 199.4 cases per year.

After an extensive investigation of severe or potentially severe cases, I identified 62 patients with at least one of the signs of cardiogenic shock. Thus, considering that 7666 cases of acute poisoning were registered in the Department of Toxicology, the prevalence of cardiogenic shock in the period 2014 - 2020 is 0.8%. Another scientific paper found a similar prevalence: "Shock in acute poisonings in children. Aetiology. Diagnostic. Treatment" - Dr. Petran Madalina, who following a statistical study carried out during 2000-2005 in the Toxicology Department of the "Grigore Alexandrescu" Children's Emergency Hospital, reported a prevalence of 0.71% of cases of cardiogenic shock out of a total of 5560 cases recorded with acute poisoning (145).

Speculating the data, we can appreciate that the prevalence of cardiogenic shock is maintained between these limits in the period 2000-2020 in the studied group.

CHAPTER 5. REGRESSION MODEL FOR PREDICTING THE SEVERITY OF ACUTE POISONING CASES BY ESTIMATING PSS IN THE EMERGENCY DEPARTMENT

5.1. Introduction. Objective

PSS (Poisoning Severity Score) allows the classification of acute poisoning cases according to severity, both in adults and children, regardless of the type and number of etiological agents involved. For classification, it is necessary to know the complete evolution of the case, considering the most severe clinical and/or paraclinical picture recorded during hospitalization. For this reason, the score is quantified retrospectively after the patient's discharge or death. The classification only considers the directly observed signs and symptoms without estimating risks based on parameters such as ingested dose or serum/plasma toxicant level. Certain symptomatic or supportive therapeutic measures such as mechanical ventilation or inotropic support may be used to assess severity. Although death is a way of evolving and not a degree of severity of intoxication, cases that result in death are graded separately on the PSS scale to allow for better accuracy in data presentation (25).

Inpatient examination of the children with acute poisoning may be within normal limits or discreetly altered, yet it may deteriorate to the point of requiring advanced treatment (7,88,89). It thus becomes necessary to identify criteria that raise the suspicion of the unfavourable evolution risk since admission so that the medical team is prepared for any scenario.

Given that PSS is a tool for retroactive assessment of the severity of the case, the premise of this study was to identify those features of each case that quantified to be able to predict the evolution of the patient from the emergency room. I wondered if I could make a statistical model to quantify the severity of the case using specific anamnestic, clinical and paraclinical indicators. Thus, based on the descriptive analysis presented in the first part of the thesis, we selected ten parameters that we considered to have the highest potential to influence the PSS prediction.

The work plan included:

1. Determining statistically significant connections between various variables: anamnestic, clinical and paraclinical indices, aetiology, gender, hospitalization length, presence of complications.
2. Develop a linear regression model and calculate the related coefficients
3. Reducing the complexity of the regression model by performing a multicriteria analysis.

5.2. Material and method

5.2.1. Batch characteristics

A batch of 62 patients aged 0-18 years with a diagnosis of acute cardiotropic poisoning complicated by cardiogenic shock was selected from cases admitted to the Department of

Toxicology and Intensive Care of the "Grigore Alexandrescu" Children's Emergency Hospital between January 2014 and December 2020.

5.3. Linear regression model

The PSS score is a standardized measure of the poisoning's severity and is the primary goal of the regression model. The immediate utility of this model is that it allows an estimation of this score right in the emergency department by grouping patients into five categories according to the PSS classification.

Of all the variables recorded in this paper, ten were selected that have the highest potential to influence the prediction of the PSS score. These are:

1. Intentional poisoning
2. ECG changes at presentation in the ER
3. The value of systolic blood pressure at presentation in the ER
4. Bradycardia
5. Coma at presentation in the ER
6. Time between exposure and examination
7. Transfer from another hospital
8. The aetiology is an insecticide
9. The aetiology is a combination of beta-blocker and calcium channel blocker
10. The value of the bases excess in the ER

The development of the regression model was done in two distinct stages. In the first stage, it was checked if the chosen variables could constitute a linear regression model, while in the second stage, the values of the model coefficients were determined. Because all the assumptions were fulfilled, a linear regression model was developed in the second stage, and the coefficients related to this model were calculated. In our case, all the coefficients are statistically significant for the model (p-value <0.05).

The equation of the regression model that returns the estimated PSS value is as follows:

Estimated PSS = **Volunteer** x 0.402 + **ECG** x 0.097 - **BPs** x 0.004 +
Coma x 0.495 + **Bradycardia** x 0.146 + **Exposure time** x 0.001–
Transfer x 0.086 + **Insecticide** x 0.499 + **BE** x 0.019 +
BBBCa x 0.565 + 2.407

However, the developed model has many independent variables and requires a long time to calculate the predicted score, making it cumbersome in some situations. To further reduce these shortcomings, we propose a multicriteria analysis that aims to predict the PSS score for poisoned patients, which can be easily applied in an emergency unit.

Multicriteria analysis is a tool for comparing and ranking different results, even if several evaluation criteria are used. It operates with several concepts, the most important of which are: option, criterion, performance matrix, score and weight (7.90).

Because AMC is developed based on the regression model, the accuracy of the estimated PSS cannot be superior to the model's accuracy; however, the short application time and ease of use recommend it instead of the regression model in the emergency units.
The application of AMC is made using the following calculation template:

Name and surname:

Intentional poisoning	Coma at presentation	BPs at presentation	Insecticide	BB+BCa	Total score	Estimated PSS score
37/0	46/0	-Value mmHg/3	46/0	52/0		(250+score)/100

CHAPTER 7. EMERGENCY ALGORITHMS FOR APPROACHING ACUTE POISONINGS WITH CARDIOTOXIC AGENTS

Lack of early diagnosis and specific treatment can lead to severe complications and even death. Given the early and late negative impact of acute poisoning among the pediatric population highlighted in previous chapters, I considered it necessary to develop some algorithms for the emergency approach of the toxic exposed cases with severe evolutionary potential.

The proposed therapeutic approach targets three major classes of drugs, frequently involved in poisonings with severe evolutionary potential, as underlined in the cases presented in extenso, respectively drugs with membrane-stabilizing effect, calcium channel blockers and beta-blockers.

The elaborated protocols are addressed to the doctors from the primary, secondary, and tertiary levels involved in managing this type of patient to facilitate an appropriate diagnostic and therapeutic approach.

The thesis presents three emergency algorithms for approaching acute poisoning cases with cardiotoxic agents:

1. Algorithm for emergency management of acute poisonings with membrane-stabilizing effect
2. Therapeutic approach algorithm in calcium channel block acute poisonings
3. Therapeutic approach algorithm in beta-blocker acute poisonings

CHAPTER 8. PERSONAL CONCLUSIONS AND CONTRIBUTIONS

The personal study was conducted for seven years in the Toxicology Department of the "Grigore Alexandrescu" Children's Emergency Hospital Bucharest, on a group of 62 patients exposed to cardiotoxic agents who associated criteria for cardiogenic shock and which I studied in detail under different aspects: epidemiological, diagnostic criteria, evolution and therapeutic manoeuvres performed.

Following the detailed statistical analysis I performed, I obtained the following conclusions:

1. The prevalence of acute poisonings complicated by cardiogenic shock in the analyzed period, 2014 - 2020, is 0.8%, a percentage similar to the reporting of a similar study conducted in the same clinic during 2000 - 2005, which reported a prevalence of 0, 71%.

2. The analysis of the epidemiological criteria identified a discrepancy in the distribution of cases according to gender. The majority of acute poisonings were registered among girls in a percentage of 75.81% compared to boys of only 24.19%, with a ratio of 3.13: 1. The age of the patients in the group ranged from 2 months to 17 years and 11 months, with a mean of 10.92 years and a standard deviation of 5.64 years. I identified a higher number of cases in urban areas (36), compared to rural areas (26), in a percentage of 58.06% and 41.94%.

3. Regarding the cases' distribution according to intention, there was almost double the number of intentional poisonings (n = 41, 66.13%) in the studied group compared to accidental ones (n = 21, 33.87%).

4. The majority of the aetiology was represented by medication (n = 50, 80.65%), unique or various combinations, while the remaining 19.35% were non-drug toxicants: methemoglobinizing substances, insecticides and abuse. The most common medication class involved was antihypertensives, found in 19 cases (14.23% of cases). This was followed by a frequency of beta-blockers and calcium channel blockers in 18 and 12 cases. These three classes of drugs represented the aetiology of 37.32% of the total cases in the group. The cases were equally divided between the multi-drug cases and those involving a single type of toxicant (31:31).

5. Regarding the time-lapsed between exposure and toxicological examination, the average time for those who go directly to SCUC Grigore Alexandrescu, a hospital equipped with a Toxicology Department, is 264.29 minutes, while the cases coming by transfer are toxicologically examined after an almost double time of 563.28 minutes. Comparing the average time between exposure to the toxicant and the time when the first medical gestures are performed on the patient, whether they are specialized or just manoeuvres to stabilize the patient, we found that both patients, the one evaluated from the beginning by a toxicologist and those who are cared for in non-specialized medical units are medically managed at similar times.

6. The patient transferred from a territorial hospital, compared to the one who presents directly in Toxicology, has a statistically significant higher risk that in the evolution of the disease to associate coma (Pearson coefficient = 0.383, $p < 0.01$), to be intubated and mechanically ventilated (0.350, $p < 0.01$) or require admission to Intensive Care (0.372, $p < 0.01$). I did not identify a link between the patient's transfer and his risk of death.

7. I also identified a quantitative correlation between the parameters of unfavourable evolution and the period of time between exposure to the toxicant and uptake by the toxicologist. Thus, the longer the period in which a poisoned patient benefits from a specialist examination, the greater the risk that he will associate coma or be mechanically intubated and ventilated, the calculated Pearson coefficients being 0.393 and 0.313 for $p < 0.01$.

8. Analyzing the signs and symptoms that outlined the clinical picture of the patients in the group, we found that the most common manifestation was drowsiness (n = 34, 54.8%), in more than half of the cases, followed by hypotension (n = 32, 51.6%) and bradycardia (n = 29, 46.8%).

9. Of all the signs and symptoms analyzed, which patients presented at admission or in evolution, I identified the strongest correlations between seizures and the risk of orotracheal intubation, with a Pearson index of 0.6. I obtained weaker but statistically significant

connections between convulsions and coma (P = 0.37), cardiorespiratory arrest (P = 0.44), the risk of admission to ATI (P = 0.36) or death (P = 0, 39). All these correlations signal the risk of complications and unfavourable evolution in the case of patients with seizures in the context of acute poisoning.

10. The most common disorder identified on the ECG, sinus bradycardia, was found only in drug poisoning (n = 16) and in no case of non-drug toxicity, most cases having a multi-drug aetiology (n = 12). The ten patients with repolarization disorders were evenly distributed between non-drug toxicants (n = 4) and medication (n = 6). Four patients in this subcategory were exposed to several toxicants simultaneously.

11. There is a statistically significant link between ventricular tachycardia and cardio-respiratory arrest with a Pearson coefficient of 0.35. Ventricular fibrillation, identified in only one case in the group that died, is also correlated with the Pearson method with mortality, with a coefficient of 0.39. There was also a link between junctional rhythm and orotracheal intubation with a coefficient of P = 0.36 and between repolarization disorders and cardio-respiratory arrest (P = 0.34).

12. The modified base excess at presentation in the ER is qualitatively correlated with the presence of grade II sinoatrial block (P = 0.44) and with repolarization disorders (P = 0.38). If the base deficit is worsened in the evolution of the case, it highlights other connections, much stronger due to the higher Pearson coefficients, with other electrocardiographic disorders. The lower the value of the base deficit, the stronger the inverse of the junctional rhythm (-0.52, Pearson) with the grade III atrio-ventricular block (-0.54 for p = 0,01) and a direct correlation to grade II sinoatrial block (0, 37 Pearson). Thus, both qualitative and quantitative correlations were identified between base excess and ECG abnormalities.

13. Base excess has proven to be an essential parameter in assessing the severity and course of severe cases of acute poisoning because I have identified many statistically significant links with heart disorders or other indicators of adverse outcomes. I noted the minimum values of the base deficit recorded in each patient's case, and we highlighted a very close inverse correlation with the risk of cardio-respiratory arrest with a Pearson coefficient of - 0.7. Also, the higher the base deficit, the higher the risk of the need for IoT (-0.55, $p < 0.01$), inotropic support (-0.53, $p < 0.01$), ATI admission (-0.48, $p < 0.01$) or mortality (-0.48, $p < 0.01$).

14. Among the analyzed cases, I identified an inverse correlation between the maximum value of potassium recorded in each patient and the presence of repolarization disorders (-0.37, $p < 0.01$) so that an increased potassium concentration decreases the risk of repolarization disorders. We also found a close direct connection (0.41, $p < 0.01$) between the maximum

amount of potassium dosed during hospitalization and the length of hospitalization. In the study group, the potassium concentration does not influence the mortality of the patients.

15. The presence of acidosis observed since the patient's admission to the hospital increases the risk of ventricular extrasystoles. The connection is strong (-0.47, $p < 0.01$), qualitative and inverse so that a pH outside the normal range, lower than 7.35, correlates with a high risk for this type of rhythm disorder. We also identified an inverse and quantitative correlation between pH and ventricular tachycardia. The lower the pH value at any time during the patient's hospitalization, the higher the risk of ventricular tachycardia (-0.39, $p < 0.01$). Regardless of its value, acidosis does not significantly influence the unfavourable evolution of the case. We identified weak links between the minimum pH value and the duration of hospitalization (0.34, $p < 0.05$) or mortality (-0.34, $p < 0.05$) and no correlation with the presence of coma, the need for inotropic support, oro-tracheal intubation or intensive care admission.

16. Analyzing the EAB parameters in the studied group, we noticed a much higher frequency of base deficit changes rather than the pH. Out of a total of 54 cases in which there were data on the pH value, only 25 of them, respectively 46.3% of the batch, presented acidosis ($n = 24$) or alkalosis ($n = 1$) at any time on during hospitalization, either at admission or in evolution. Regarding the base deficit, although there were data for only 48 patients, I noted abnormalities in 70.8% of them ($n = 34$). I thus concluded that the base deficit is a much more sensitive parameter in the studied group than the pH.

17. The average length of hospital stay is 4.42 days with a standard deviation of 2.35 days. Most patients in the study group ($n = 15$) were discharged after three days. The range ends of the hospitalization stay length were noted in a patient with unintentional acute poisoning with insecticide discharged after 15 days and an adolescent evaluated only in the emergency department and transferred to another medical unit.

18. We identified a minor inverse correlation with a Pearson coefficient of -0.282 between hospitalization and mortality. The higher the length of the hospital stay, the lower the mortality, suggesting that the highest risk of death is immediately post-exposure. Once the patient exceeds an initial critical period, the chances of a favourable outcome increase significantly.

19. Of the 59 patients in whom there were data on intestinal decontamination, in 26 of them, respectively in 44.07%, gastric lavage was performed, although in only 4 of them, the manoeuvre was performed in the first hour after ingestion, according to the protocol. In the other 23 cases, no method of gastrointestinal decontamination was practised because the time

of presentation at the hospital was beyond the first hour after ingestion when the risk-benefit ratio contraindicated the manoeuvres.

20. Orotracheal intubation and mechanical ventilation (OTI – MV) was required by 14 patients (22.58% of the group). The indications for these manoeuvres were: significant respiratory depression not responding to oxygen, cardiovascular insufficiency, altered state of consciousness with loss of airway protection reflexes and/or seizures refractory to drug therapy.

21. Inotropic supportive treatment with vasopressor amines was administered in 10 of the 62 cases of severe intoxication in the group (16.13%). Eight of the 10 cases were multi-drug intoxications, and in only 2 cases, the aetiology was represented by a single drug, namely an alpha2-sympathomimetic agonist and a benzodiazepine. There is an interesting finding in patients with inotropic support; half of them (n = 5) have a combination of beta-blocker and calcium channel blocker as aetiology.

22. Almost half of the patients in the study group (n = 30, 48.39%) required ATI monitoring and treatment, an argument favouring the severity of acute cardiotropic poisoning cases associating signs of cardiogenic shock. Since admission, 27 cases showed signs of severity or anamnesis revealing exposure to potentially severe toxic agents, so they were directed straight from the Emergency Department to the ATI. However, three of the cases were initially hospitalized in the Department of Toxicology and later referred to Intensive Care because their condition progressively deteriorated in evolution.

23. The average length of hospital stay in the ICU was 1.8 days, with a cumulative number of all cases of 54 days. The most extended period of admission to ATI was in a 3-year-old patient with unintentional acute carbamazepine poisoning, who on the sixth day of admission had an irreversible cardio-respiratory arrest during resuscitation manoeuvres.

24. When analyzing the studied group according to the severity calculated by applying the standardized PSS scale, we found that most investigated cases (n = 37) were severe forms (PSS = 3), a percentage of 59.68% of the group. Eighteen cases were moderate (29.03%), while seven patients died and were classified as PSS = 4.

25. Following the mortality analysis, we recorded seven deaths, representing 11% of the group. The ingestion of the toxicant caused all seven deaths, two due to medication ingestion and the rest due to exposure to toxic pesticides: one case with herbicide, one case with carbamate insecticide - Furadan and 3 cases with organophosphorus insecticide - Diazinon.

26. The distribution of pesticides among deaths was homogeneous for most of the evaluated epidemiological parameters, without identifying a predominance for gender, age, the

environment or intention. I have not identified a statistically significant connection between pesticide exposure and death, a conclusion made after running a chi-square test. One argument in this regard is that of the 9 cases in the group exposed to pesticides, five died while another four survived.

27. All deceased patients were monitored and treated in ATI, two of them being subsequently transferred after initial admission to Toxicology, where their condition deteriorated. All seven patients were also intubated and mechanically ventilated. The most extended period of hospitalization in Intensive Care, six days, was recorded in the case of acute carbamazepine poisoning, the patient being also OTI-MV since Grigore Alexandrescu ER, where he presented cardio-respiratory arrest. The majority of deaths, 5 out of 7 cases, occurred within 1-2 days of hospitalization, suggesting the particular toxicity of the etiological agents.

28. I developed a linear regression model that uses ten independent variables to predict the value of the PSS score from the ER. The model was the basis of a multicriteria analysis (MCA) that can be easily applied in the emergency room for any patient poisoned with cardiotoxic agents because he uses only five variables and a calculation template to estimate the PSS score. Because MCA is derived from the regression model, its accuracy is up to 75%, which is a compromise between the complexity of the regression model and its accuracy.

Chapter 9. ORIGINALITY OF THE THESIS

This doctoral thesis aims and conducts an extensive study of acute poisoning with cardiotoxic agents complicated by cardiogenic shock in the pediatric population, performing a detailed and extensive analysis in terms of epidemiology, diagnostic criteria and applied therapeutic measures.

The first section of the thesis presents the results of an extensive bibliographic study following which I noticed a shortage of scientific papers to address this pathology in the pediatric population; the identified materials are often limited to clinical case reports or small series of cases while treatment protocols are based on the consensus of toxicologists rather than evidence-based medicine.

Thus, due to the low incidence of severe poisonings complicated by cardiogenic shock in children, the possibility of conducting a randomized controlled trial to demonstrate the efficacy of these protocols is challenging to implement. However, the personal study results reinforce the already existing conclusions in the literature.

The personal section of the thesis carried out a descriptive study of a group of 62 patients diagnosed with acute poisoning with cardiotoxic agents who associated signs of cardiogenic shock, recruited from among the cases admitted to the Department of Toxicology - Intensive Care of the Emergency Clinical Hospital for Children "Grigore Alexandrescu" Bucharest. The analysis of the cases revealed a diversity of the registered parameters, which allowed the possibility to study the epidemiological, clinical and paraclinical characteristics in detail. The results thus obtained allowed correlations related to patients' evolution, severity and prognosis.

In the second section of my personal research, I investigated the possibility of predicting the evolution of a patient from the emergency room (ER) based on the features identified after his examination. Current assessment methods of the case severity are based on the PSS score, which is a tool for retroactive evaluation. I thus developed a linear regression model that uses ten independent variables to predict the value of the PSS score since the ER. The model has a high degree of complexity, making it challenging to apply in the emergency room, where the intervention time is critical. For this, starting from the validated linear regression, a multicriteria analysis (MCA) was performed, which can be easily applied to any patient exposed to cardiotoxic agents because he uses only five variables and a calculation template to estimate the PSS score. Because MCA is derived from the regression model, its accuracy is up to 75%, which is a compromise between the complexity of the regression model and its accuracy.

The thesis also includes an extended presentation of three cases of acute multi-drug poisoning with beta-blockers and calcium channel blockers. The comparative analysis of the cases draws attention to the different evolutionary aspects that may derive from the same aetiology, a solid argument for the thorough follow-up and timeliness of the intervention in this type of cases.

At the end of the thesis are presented in detail three models for emergency therapeutic approach algorithms of the poisoning with beta-blockers, calcium channel blockers and membrane-stabilizing effect agents, which will be helpful in pediatric toxicological practice.

Through the presented results, this doctoral thesis represents a premiere for our country through the diversity of the analyzed parameters, being published in the context of a deficit of scientific studies aiming at the pediatric population. The novelty proposal is the regression model developed to predict the value of the PSS severity score immediately after evaluating the patient in the emergency department. Of particular practical value are the proposals for

algorithms for urgently addressing cases of exposure to toxic substances with severe evolutionary potential in order to streamline the therapeutic and diagnostic approach.

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- TWO CASES OF FATAL POISONING DUE TO CARDIOTOXIC AGENTS

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- EPIDEMIOLOGICAL STUDY OF ACUTE POISONING WITH CARDIOTOXIC DRUGS IN CHILDREN

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