GRIGORE T. POPA UNIVERSITY OF
MEDICINE AND PHARMACY IASI

HABILITATION THESIS

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Associate Professor

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A poisonous story: from diagnostic to therapeutic challenges in internal medicine

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CONTENTS

ABBREVIATION LIST

AAPCC, American Association of Poison Control Centers
ABG, arterial blood gases
AC, activated charcoal
ACLS, advanced cardiac life support
ACMT, American College of Medical Toxicology
ACS, acute coronary syndrome
ADA, American Diabetes Association
AHF, acute heart failure
AIVR, accelerated idioventricular rhythm
AKI, acute kidney injury
ALD, alcoholic liver disease
ALF, acute liver failure
ALP, alkaline phosphatase
ALS, advanced life support
ALT, alanine transaminase
AoVmax, aortic maximal velocity
AP, acute pancreatitis
APACHE II, Acute Physiology and Chronic Health Evaluation
APE, acute pulmonary edema
AR, alkali reserve
ARDS, acute respiratory distress syndrome
ARF, acute respiratory failure
AST, aspartate transaminase
AUC, area under the curve
AV, atrioventricular
BChE, butyrylcholinesterase
BEL, blood ethanol level
BGL, blood glucose level
BMI, body mass index
BNP, brain natriuretic peptide
BP, blood pressure
BUN, blood ureea nitrogen
CBC, complete blood cell count
CBS, cardiopulmonary bypass support
CCB, calcium channel blocker
CCU, coronary care unit
ChEs, plasma cholinesterase
CI, confidence intervals
CIS, cholinesterase inhibitor substances
CK, creatin kinase
CKMB, MB isoenzyme of creatine kinase
COHb, carboxyhemoglobin
CPR, cardiopulmonary resuscitation
CRP, C-reactive protein
CTP, Child-Turcotte Pugh
CTU, Cardio-Thoracic Unit
CV, coefficient of variation
CVVH, continuous veno-venous hemofiltration
DBP, diastolic blood pressure
DIHC, drug-induced hypoglycemic coma
DIP, drug-induced pancreatitis
DM, diabetes mellitus
DT, deceleration time
ECMO, extracorporeal membrane oxygenation
ECV, electrical cardioversion
ED, Emergency Department
EDT, E-wave deceleration time
EMCDDA, European Monitoring Centre for Drugs and Drug Addiction
ER, Emergency Room
FBG, fasting blood glucose
FiO2, fraction of inspired oxygen
FLF, fulminant liver failure
GCS, Glasgow Coma Scale
GFR, glomerular filtration rate
GGO, ground glass opacities
GGT, gamma glutamyl transpeptidase
GL, gastric lavage
GOT, glutamic-oxaloacetic transaminase
GPT, glutamic-pyruvic transaminase
GSH, hepatic glutathione
HDI, high-dose-insulin therapy
HE, hepatic encephalopathy
HGN, hepatic gluconeogenesis
HIE, hyperinsulinemia/euglycemia
HR, heart rate
IABP, intra-aortic balloon pump
ICU, Intensive Care Unit
IFG, impaired fasting glucose
IGT, impaired glucose tolerance
IHN, isonicotinic acid hydrazide
ILE, intravenous lipid emulsion
IQR, interquartile range
IR, insulin resistance
IVC, inferior vena cava
IVS, interventricular septum
KDIGO, Kidney Disease: Improving Global Outcomes
LAD, left anterior descendent coronary artery
LDH, lactate dehydrogenase

LET, lipid emulsion therapy
LRT, lipid resuscitation therapy
LT, liver transplantation
LVEF, left ventricular ejection fraction
LVSF, left ventricle shortening fraction
MAG, mean absolute glucose
MAGE, mean amplitude of glycemic excursions
MARS, Molecular Adsorbent Recirculating System
MELD, Model for End-stage Liver Disease
MGL, mean glucose level
MI, myocardial infarction
MLR, monocyte-lymphocyte ratio
NAC, N-acetyl-cysteine
NAD, nicotinamide adenine dinucleotide
NLR, neutrophil-lymphocyte ratio
NSAIDs, nonsteroidal anti-inflammatory drugs
NSTEMI, non-ST segment elevation acute myocardial infarction
NT-proBNP, N-terminal prohormone of brain natriuretic peptide
NYHA, New York Heart Association
OGTT, oral glucose tolerance test
OHA, oral hypoglycemic agent
OIC, optimal intensive care
OP, organophosphates
OR, odds ratios
OTCs, over-the-counter medicines
PaO2, partial pressure of arterial oxygen
PCCs, Poisoning Control Centers
PEA, pulseless electrical activity
PLR, platelet-lymphocyte ratio
PSS, poisoning severity score
RBBB, right bundle branch block
RBC, red blood cell
RCA, right coronary artery
RDW, red cell distribution width
ROC, receiver operating characteristic
SBP, systolic blood pressure
SCD, sudden cardiac death
SD, standard deviation
SII, systemic immune inflammation index
STEMI, ST segment elevation acute myocardial infarction
TdP, torsade de pointes
TMP-SMX, trimethoprim-sulfamethoxazole
TnI, troponin I
TTE, transthoracic echocardiography
VF, ventricular fibrillation
VT, ventricular tachycardia
WBC, white blood cells
WCT, wide complex tachycardia

ABSTRACT

The habilitation thesis entitled "**A poisonous story: from diagnostic to therapeutic challenges in internal medicine**" provides an overview of my professional, academic and scientific activity in the postdoctoral period (2003-2022) at the "Grigore T. Popa" University of Medicine and Pharmacy Iași. This thesis illustrates some of my major directions of postdoctoral scientific research and represents the basis needed to obtain the habilitation, allowing me to coordinate Ph.D. students. Following a detailed overview of my main research focuses, I also included in this thesis a description of a set of forthcoming research directions which I intend to follow in the near future has also been included in this thesis.

As recommended and approved by the National Council for Attestation of Titles, Diplomas, and Certificates (CNATDCU), the present thesis is structured in three main sections, as follows:

Section I – Scientific achievements over the postdoctoral period.

Section II – Directions for the development of scientific, professional and academic activity.

Section III – References.

Section I begins with a summary of my professional, academic, and scientific achievements over the past 18 years after having obtained the PhD title, and continues with the presentation of the major research directions to which I have contributed. Throughout my professional career, my clinical and academic work intertwined and developed in parallel and on several levels in the field of internal medicine, cardiology, clinical and experimental toxicology. Thus, the synthesis of the most important 85 articles that I authored and that were published in journals indexed in both Thomson ISI Web of Science Core Collection (50), as well as in international databases (35) presented in the habilitation thesis reflects my attempt to integrate the novelties discovered in the field of internal medicine and cardiology to the clinical toxicology field. These articles have obtained a total of 189 citations in Clarivate Analytics Web of Science Core Collection publications and 592 citations in Google Scholar, thus generating a Hirsch-index of 10 according to Clarivate Analytics.

Chapter I comprises the results of the most important research related to the role of biomarkers and multimodality imaging in the early diagnosis and outcome prediction for patients admitted in an Internal Medicine department. My main scientific preoccupations were: the role of traditional and new biomarkers for the outcome prediction in patients admitted with an acute condition (i.e., acute poisoning, acute decompensated chronic heart failure and SARS-CoV-2 infection), multimodality imaging as complementary method for diagnosis and outcome prediction, including the role of regular and new laboratory methods in diagnostic evaluation of poisoned patients, and the role of vitamin D in systemic illnesses. Also, this chapter includes the models developed for risk assessment based on statistical methods, which identified valuable predictors and attained an accurate risk stratification in acutely poisoned patients. These results were presented in 11 ISI indexed articles and 6 articles indexed in international databases. Some of the aforementioned scientific aspects were published in a book chapter I authored, entitled "Toxic and drug-induced changes of the electrocardiogram" published by InTech Open. The chapter has 28 citations in international databases.

Chapter II focuses on the role of modern therapies in the management of acute poisoning, including research on lipid emulsion therapy (LET) in cardiovascular drugs overdose, the Molecular Adsorbent Recirculating System (MARS) use in poisoning with Amanita Phalloides and the use of neutralizing agents for pesticide poisoning. These results were published in 4 ISI indexed articles and 1 paper indexed in international databases.

Chapter III reviews the research and the original contribution I have brought in the field of clinical toxicology, with a focus on challenges encountered in the diagnosis and therapy of medical emergencies direct linked by the effects of drugs overdose and nonpharmaceutical agents' exposure on several organs and systems, with the focus on pharmaceuticals, toxins, and food components. The main aspects covered in my research were rhabdomyolysis, cardiovascular complications after acute exposure to drugs and poisons, metabolic consequences of acute poisoning, hepatotoxicity, and rare complications after exposure to drugs and environmental agents. Furthermore, I included the main epidemiological aspects regarding acute poisoning in Iași county. This chapter brings together the results of 12 ISI indexed articles and 19 indexed articles in international databases.

Section II describes several directions I plan to focus on while developing the three professional areas fundamental in my career: the scientific research activity, the professional activity and the academic activity. I intend to focus my forthcoming scientific activity on researching the influence of COVID-19 pandemic on the pattern of medical emergencies, including acute poisonings in North-Eastern Romania. The identification of new risk-predictors and scores useful to improve the management of patients with medical conditions and SARS-COV2 infection is another topic of my interest. The research regarding the role of vitamin D in inflammatory and cardiovascular diseases was already begun, with a thorough review, but new directions will be pursued. Studies regarding multimodality diagnostic methods and the role of modern therapies in patients admitted for medical emergencies will also be an area of interest. Also, I will continue to explore the subjects which were my main research preoccupation in the past twenty years, such as cardio-metabolic interrelations in patients with cardiovascular conditions and/or cardiovascular risk, the biomarkers in poisoned patients and those admitted with a medical urgency and emergency as well as new and emerging imagistic techniques and therapies for medical patients, taking into account the potential influences exerted by our therapeutic intervention. When it comes to scientific research, I intend to involve the doctoral students interested in the study of the topics presented in this habilitation thesis, but also in other research directions I have worked on. In addition to completing the teaching activity and textbook projects for students and resident doctors, I propose the continuous organization of training courses in the field of internal medicine and clinical toxicology, including the reintroduction of the interdisciplinary master program "Clinical toxicology – at the crossroads of medical specialties" in the educational offer of the "Grigore T Popa" University of Medicine and Pharmacy Iași.

Section III includes a number of 747 references used for the preparation of this thesis and the elaboration of all papers included here.

REZUMAT

Teza de abilitare intitulată "O poveste cu iz toxic: de la provocările diagnostice la cele terapeutice în medicina internă" trece în revistă activitatea mea profesională, academică și științifică din perioada postdoctorală (2003-2022) în cadrul Universității de Medicină și Farmacie "Grigore T. Popa" din Iași. Teza include câteva dintre direcțiile mele majore de cercetare postdoctorală și reprezintă suportul necesar pentru a obține abilitarea de a coordona studenți doctoranzi. Au fost incluse în teză și descrierea unor direcții de cercetare ulterioară, pe care intenționez să le dezvolt în perioada imediat următoare.

Teza este structurată în trei secțiuni mari, conform criteriilor recomandate și aprobate de către Consiliul Naţional de Atestare a Titlurilor, Diplomelor si Certificatelor Universitare (CNATDCU):

Secțiunea I – Realizări științifice din perioada postdoctorală.

Secțiunea II – Proiecte viitoare în activitatea științifică.

Secțiunea III – Referințe.

Prima secțiune a tezei de abilitare începe su o scurtă trecere în revistă a principalelor realizări profesionale, academice și științifice din ultimii 18 ani, după obținerea titlului de doctor în științe medicale. În continuare, am prezentat direcțiile majore de cercetare la care am contribuit. De-a lungul carierei mele profesionale, activitățile în clinică și în zona academică au fost strâns legate și s-au dezvoltat în paralel, pe mai multe paliere în domeniul medicinei interne, cardiologiei, toxicologiei clinice și experimentale. Astfel, sinteza a celor mai importante 85 articole publicate în reviste indexate atât în Thomson ISI Web of Science Core Collection (50), cât și în bazele de date internaționale (35) prezentate în teza de abilitare reflectă încercările mele de integrare a noutăților din domeniul medicinei interne și cardiologiei în domeniul toxicologiei clinice. Aceste articole au fost citate de 189 de ori în publicații indexate în Clarivate Analytics Web of Science Core Collection și au obținut 592 citări în Google Scholar, astfel contribuind la un indice Hirsch de 10, conform Clarivate Analytics.

Capitolul I se referă la rezultatele celor mai importante cercetări asupra rolului biomarkerilor și a imagisticii multimodale în diagnosticarea precoce și evaluarea prognostică a pacienților internați într-un department de medicină internă. Preocupările principale au vizat rolul biomarkerilor tradiționali și nou apăruți în predicția prognosticului pacienților internați pentru o boală acută (de ex. intoxicația acută, decompensarea acută a insuficienței cardiace cronice, infecția cu virus SARS-CoV-2), metodele de imagistică multimodale ca mijloace complementare pentru diagnostic și apreciere a prognosticului, rolul metodelor de laborator clasice și nou apărute în evaluarea diagnostică a pacienților cu intoxicații acute, precum și rolul vitaminei D în bolile sistemice. De asemenea, am inclus în acest capitol dezvoltarea unor modele de evaluare a riscului, pe baza metodelor statistice, care au permis identificarea unor predictori valoroși pentru stratificarea corectă a riscului la pacienți cu intoxicații acute. Aceste rezultate au fost publicate în 11 articole indexate ISI și 6 articole indexate în bazele de date internaționale. De asemenea, o parte dintre datele științifice studiate în această perioadă au fost publicate într-un capitol de carte, publicat de InTech Open, o editură internațională open-access, care a fost citat de 28 de ori în bazele de date internaționale.

Capitolul II abordează rolul terapiilor moderne în managementul intoxicațiilor acute. Am studiat terapia cu emulsie lipidică în intoxicațiile cu medicație cardiovasculară, sistemul MARS (dializa hepatică) în intoxicații cu Amanita phalloides și rolul terapeutic al unor agenți neutalizanți în intoxicațiile cu pesticide. Aceste cercetări au fost publicate în 4 articole indexate ISI și un articol indexat în baze internaționale de date.

Capitolul III include cercetările și contribuțiile originale aduse în domeniul toxicologiei clinice, fiind centrat cu precădere asupra problemelor de diagnostic și tratament al urgențelor

medicale legate de efectele intoxicațiilor acute medicamentoase și nemedicamentoase asupra organelor și sistemelor, grupate în efecte ale medicamentelor, toxinelor și compușilor alimentari. Aspectele principale asupra cărora s-a orientat cercetarea mea au fost rabdomioliza, complicațiile cardiovasculare după expuneri acute la medicamente și toxine, concecințele metabolice ale intoxicațiilor acute, hepatotoxicitatea, precum și complicațiile rare după expunerea la droguri și la agenți din mediul înconjurător. De asemenea, am inclus și principalele aspecte de epidemiologie ale intoxicațiilor acute din județul Iași. Acest capitol reunește rezultatele a 12 articole indexate ISI și 19 articole indexate în bazele de date internaționale.

Secțiunea a II-a include descrierea unor proiecte pe care îmi doresc să la dezvolt în cele trei domenii fundamentale ale carierei mele: activitatea de cercetare științifică, activitatea profesională medicală și cea academică. Intenționez să abordez în următoarea perioadă de cercetare subiecte precum influența pandemicei de COVID-19 asupra pattern-ului urgențelor medicale și a intoxicațiilor acute în regiunea noastră, identificarea unor noi predictor de risc și/sau scoruri pentru a îmbunătăți managementul pacienților cu patologii medicale care asociază infecția cu virus SARS-COV2, sau rolul vitaminei D în bolile inflamatorii și cardiovasculare, cercetare pe care am început-o deja prin realizarea unui review extins, publicat recent. Studii cu privire la modalități combinate de diagnostic și rolul noilor terapii la pacienții cu patologii medicale vor reprezenta o altă preocupare. Intenționez să continui să abordez în activitatea științifică viitoare subiecte privind interrelații cardio-metabolice la pacienții cu patologie cardiovasculară și/sau cu risc cardiovascular, rolul biomarkerilor la pacienți internați pentru urgențe medicale sau intoxicații acute, care au reprezentat preocupări în ultimii 20 de ani. Nu în ultimul rând, voi continua cercetările cu privire la rolul metodelor imagistice și terapeutice noi în managementul pacienților cu patologii medicale, având în vedere impactul potențial al acestor noi metode terapeutice. În cercetarea științifică, voi antrena doctoranzii interesați în domeniile prezentate în cadrul acestei teze de abilitare, dar și în alte direcții de cercetare pe care le-am abordat în activitatea mea. În plus față de activitaea didactică și proiectelor de carte pentru studenți și medici rezidenți, îmi propun organizarea unor cursuri de perfecționare în domeniul medicinei interne și toxicologiei clinice, inclusive reintroducerea, în cadrul programelor de masterat ale Universității de Medicină și Farmacie "Grigore T. Popa" din Iași, a programului interdisciplinar de masterat ”Toxicologia clinică – la confluența specialităților medicale”.

Secțiunea a III-a include un număr de 747 referințe bibliografice utilizate pentru redactarea acestei teze și elaborarea tuturor articolelor incluse în această prezentare.

OVERVIEW OF PROFESSIONAL, ACADEMIC AND SCIENTIFIC CONTRIBUTIONS

A medical career was my only option since high school. The training and skills obtained during my four years in mathematics-physics profile at the "Costache Negruzzi" High School was in harmony with my personality and preferences. As a student of General Medicine Faculty, I was inspired to pursue an Internal Medicine specialty by my most prominent teachers in Internal Medicine, Lecturer Dr. Georgeta Scripcaru and Prof. Dr. George Popa. Notably, the mentoring and guidance, since my fourth year of medical school, from the late Prof. Cezar Daniil resulted in my graduation thesis "Percutaneous transluminal angioplasty of iliac and femoral arteries" presented in September 1989. During my clinical internship and then residency of Internal Medicine in the Emergency Clinic Hospital Iași, I was actively involved in the complex evaluation of medical emergencies, including toxicological emergencies, because the clinic was the referral center for clinical toxicology in North-Eastern Romania. My mentors during this period were the late Lecturer Dr. Valeria Hurjui and Lecturer Dr. Mihai Frasin, the chiefs of the Emergency Medical Clinic during that time. Another significant influence for my future development and choice for specialty was the short internship I had in the Cardiology Clinic of the "Sf. Spiridon" County Hospital, under direct supervision of the late Prof. Dr. Mihai Dan Datcu, where I became aware of the complexity and challenges in managing cardiovascular patients. All these experiences had an essential contribution in my future professional choices and domains of research as well as in the research I published.

Professional activity

I've graduated the Faculty of General Medicine of the Institute of Medicine and Pharmacy Iași, currently the "Grigore T. Popa" University of Medicine and Pharmacy (Bachelor's degree diploma H 1015/no.40/24.10.1989), with the overall mean of 9.97 (personal scholar record, scholar registry excerpt no. 8688).

My professional career started in December 1989 as a medical intern at the „Dr. C. I. Parhon" Clinical Hospital No.2 in Iași. I have worked during that period in Pediatric, Obstetric Gynecology and Internal Medicine departments of the respectively "Sf. Maria" Pediatric Hospital, the "Cuza Vodă" Clinical Hospital and the "Sf. Spiridon" Clinical County Hospital. In September 1991, I obtained, after an exam, a junior assistant position, within the Discipline of Internal Medicine at the Faculty of Medicine of the "Grigore T. Popa" University of Medicine and Pharmacy Iasi, which marked the beginning of my teaching career.

In 1991 I became a resident physician in Internal Medicine in the Medical Clinic of the Emergency Clinical Hospital Iași (order of the Ministry of Health no.1711/October 19, 1991). During the residency period, I was dedicated to obtaining a wide range of clinical skills and performances, given the complexity of the Internal Medicine specialty and I realized that the study of internal medicine could offer me a comprehensive perspective on the patient and a more complex approach to his pathologies. Nonetheless, the toxicological emergencies referred to our hospital (which was, during that time, a regional tertiary center for toxicological pathology) and a wide range of medical and surgical emergencies addressed to the hospital were major professional and human challenges, which contributed to what I am today as a clinician. In 1992, I attended the postgraduate lectures of Internal Medicine and I've graduated in 1992, after a practical and theoretical exam (diploma I 5253/no.70/15.04.1993). In 1994, I was confirmed as a specialist physician in Internal Medicine by Order of the Health Ministry no. 2214 from December, 1994. I have received the clinical integration in the Emergency Medical Clinic of the Emergency Clinical Hospital Iași since October 1995.

Working in an Emergency Hospital at a period when Emergency Medicine was not available as a distinct medical specialty in Romania, made me eager to develop clinical and technical abilities for an adequate professional response. As a result, techniques of resuscitation, orotracheal intubation, the management of a patient with shock, hypothermia, polytrauma, acute poisoning, were achieved not only by theoretical knowledge, but also after the postgraduate lectures and practical internship in Emergency and Catastrophe Medicine in 1996, at the Pilot Center for Assistance of Medical Emergencies in Târgu Mureș, organized by the Society of Emergency and Catastrophe Medicine, University of Medicine and Pharmacy Târgu Mureș, French Embassy in Bucharest, with the support of the University Paris XII Val de Marne, French Medical Military School Val de Grace and Medical Services of the Paris Firefighters Brigade, under the supervision of both Raed Arafat M.D. and Prof. Dr. M. Chiorean, head of the ICU Department of the Clinical County Hospital of Târgu Mureș (diploma accredited by the Romanian National Education Ministry and the University Paris XII). Also, I've attended the postgraduation lecture of "Modern drug additions – diagnostic, treatment, prevention" organized by Psychiatry and Drug Addiction Department of the "Grigore T. Popa" University of Medicine and Pharmacy Iași, which I've graduated in March, 1997 (diploma M 001646/ no. 1106/31.03.1997).

In 1994, I was admitted as a doctoral student, starting my studies under the coordination of Prof. Dr. Jan Hurjui. My doctoral thesis had the title "Hypoglycemia in acute exogenous poisoning which affect the liver", consisting in a retrospective study of 15,497 cases of acute poisoning, a prospective study of 1,034 patients with acute poisoning with hypoglycemia, as a result of acute poisoning, and an experimental study, which attempted to synthetize and characterize two new original methionine derivatives as antidotes for acetaminophen acute experimental poisoning in rats. The public defense of the doctoral thesis was held on October 19, 2002, acknowledging me as a Doctor in Medicine by the Order of the Ministry of Education and Research in April 24, 2003 (diploma Series C No. 0005573).

During the following years, I've attended numerous lectures, congresses and conferences in Romania and abroad, organized by the Romanian Society of Internal Medicine, Romanian Society of Cardiology, Romanian Society of Pneumology, Romanian Society of Pharmacology, Therapeutics, and Clinical Toxicology, Romanian Society of Hypertension, European Heart Rhythm Association, International Society of Cardiovascular Pharmacotherapy, European Society of Cardiology, and European Association of Cardiovascular Imaging. In 1999, following the board certification exam, I have become a senior physician in Internal Medicine, confirmed by Order of the Health Ministry no. 637 from June, 1999 (certificate Series P1 no.012010).

Hospital organization and the needs of the clinic required the presence of a specialist in Cardiology, and as a result, I began the training in the second specialty – Cardiology, in the former Cardiology Center in Iași, currently the Institute of Cardiovascular Diseases "Prof. Dr. George IM Georgescu". I became a specialist physician in Cardiology, confirmed by Order of the Health and Family Ministry no. 500 from April 30, 2004. The practical skills obtained during this second residency in Cardiology, in the Echocardiography Laboratory of the Medical Cardiology Clinic, under the direct supervision of the late Prof. Dr. George I.M. Georgescu and Prof. Dr. Cătălina Arsenescu Georgescu, allowed me to obtain the competence of General Echocardiography, after the certification exam (Certificate Series C 013831, No.15561/02.06.2004). Starting with 2004, I was responsible for the echocardiography examinations and other non-invasive diagnostic tests (Holter monitoring, ABPM, ECG stress test) for the Internal Medicine Clinic and surgical clinics of the hospital.

From March 15, 2001, to November 1st, 2002, I was appointed Chief of the Medical Clinic of the Emergency Clinical Hospital, Iași. This position was assigned later to Prof. Dr. Șorodoc Laurențiu.

I've followed my interests, continuously perfecting my professional knowledge, and acquired new skills by attending training courses in the country and abroad, credited by the Medical College of Romania, in different areas of internal medicine and cardiology, with a special mention for the lectures "**Cerebral involvement in internal diseases**" by the Romanian Society of Internal Medicine, in 2007, the EAE Educational Courses „**Doppler echocardiography – from basics to advanced applications**" in 2007 and „**Clinical applications of echocardiography: old and new**" in 2010.

Since 2011, after a series of administrative reorganizations, the Medical Clinic of the "Sf. Ioan" Emergency Hospital Iași became the IVth Internal Medicine Clinic of the "Sf. Spiridon" Clinical County Emergency Hospital, currently the IInd Internal Medicine Clinic of the same hospital, where I work today.

Academic activity

After university graduation, I became a member of the academic community in 1991, junior assistant by competition at the Emergency Medical Clinic – Internal Medicine Discipline, of the Faculty of Medicine of "Grigore T. Popa" University of Medicine and Pharmacy Iași and I've started teaching 4th year Romanian and later English students in the Emergency Medical Clinic of the Emergency Hospital Iași. The course of my career in university education so far included the following steps, all obtained after competition and exams:

- 1991 - 1994: Internal Medicine Junior Teaching Assistant
- 1994 - 2005: Internal Medicine Assistant Professor in the Discipline of Internal Medicine (Medical Emergencies - Toxicology)
- 2005 – 2015: Internal Medicine Lecturer in the Discipline of Internal Medicine, Toxicology (Internal Medicine, Toxicology, Clinical Toxicology)
- 2015 – present time: Internal Medicine Associate Professor in the Discipline of Internal Medicine, Toxicology (Internal Medicine, Toxicology, Clinical Toxicology)

I completed my didactic training by attending the postgraduation lecture of Psycho-Pedagogy in 1997 organized by the Department of Didactic Personnel Training (Certificate no. 96117/05.06.1997), and acquiring foreign language competence (English level B2+) in 2010 (Certificate. No. 952/24.09.2010), granted by the English Department and Center of Foreign Languages and Continuous Education from the Faculty of Letters, of the "Alexandru Ioan Cuza" University Iași. The transition from an assistant professor to a lecturer involved the ability to communicate the information easily with attendees, to adapt my vocabulary to that of the audience, to respond accurately and clearly to questions. To overcome my limits, I attended and successfully completed the "Advanced Presentation Skills Program" in May, 20-22th, 2010 (certificate awarded by Personal Consulting), and Nucleus Academy I "The Trainer" (how to design a CV CME course) in 2010, October, 16th-18th, in Istanbul, Turkey.

Thus, since 1991 and until now I have carried out teaching activities (internships and courses) and guidance at the Faculty of Medicine – General Medicine specialty and General Medical Assistance, both in Romanian and English. I have coordinated numerous bachelor's theses in Romanian and English at the Faculty of Medicine (General Medicine and General Medical Assistance). Also, between 2014 and 2016 I organized workshops of electrocardiography for basic and advanced skills, involving 4th year students attending English Program of the Faculty of Medicine.

I have coordinated the residents within the Internal Medicine residency program, and modules of Internal Medicine of Dermatology, Rheumatology, Pneumology, Cardiology, as well as Family Medicine residents, since 1999. Starting with 2006, I've been nominated as accredited coordinator for the tuition program of residency in the second related specialty, in the University center of Iași, for the cardiology and internal medicine specialties (order of the Ministry of Health no.180/02.03.2006, completed with the order of the Ministry of Health no. 1309/30.10.2006).

Between 2005 and 2011, I was lecturer of the multidisciplinary Master Program "CLINICAL TOXICOLOGY" organized by the Faculty of Medicine of "Grigore T. Popa" University of Medicine and Pharmacy Iași, which had ARACIS accreditation. During this period, I was involved in guiding dissertations of several graduates of the master program. In 2007, I was one of the lecturers of the postgraduate program "Cardio-respiratory resuscitation in particular situations" which took place between October and December 2007.

At the university's request, I acted as commission member or committee chair of the various exams and competitions: member in the commissions for obtaining the title of specialist and senior specialist in Internal Medicine and Family Medicine, member of the commissions in competitions for teaching positions, member of doctoral admission commissions or doctoral study guidance commissions. I have repeatedly participated in the organization of Medical School Admission exam and Bachelor's examination, at the "Grigore T. Popa" University of Medicine and Pharmacy Iași, as well as in the organization of residency competitions.

I coordinated and I participated as an invited speaker to a broad range of postgraduation academic lectures organized by the "Grigore T. Popa" University of Medicine and Pharmacy, Iași, the Medical College or other professional societies and associations. I am frequently invited to speak and share my clinical and academic experience during various medical congresses and conferences in the country and abroad, serving the interests of both my specialty and other medical fields (internal medicine, cardiology, clinical toxicology, family medicine, etc.). Since 2006, I have been a constant invited speaker of the National Congress of the Romanian Society of Internal Medicine.

I contributed with several lectures and workshops and I was also involved in the organization and scientific program in the 2019 Summer School of the Young Internists: "Hands on" in cardio-respiratory explorations, and in the 2021 Internal Medicine School: Updates in cardiovascular pathology online, organized by the IInd Internal Medicine Clinic of the "Sf. Spiridon" Clinical County Emergency Hospital under the patronage of the Grigore T. Popa" University of Medicine and Pharmacy, Iași.

I am a member of multiple professional societies:

- Member of the Society of Physicians and Naturalists Iași – Internal medicine and Cardiology section; I served as a secretary of this section between April, 2007 – September, 2011.
- Member of the Romanian Society of Internal Medicine and European Federation of Internal Medicine.
- Member of the Romanian Society of Pharmacology, Therapeutics and Clinical Toxicology.
- Member of the Romanian Society for the Study of Chemotherapeutics, Iași.
- Member of the Romanian Society of Cardiology (Working Group of Emergency Cardiology, and Working Group of Ischemic Cardiopathy) and ESC.
- Fellow of the American College of Chest Physicians since 2011.
- Member of the International Society of Cardiovascular Pharmacotherapy.
- Member of the Romanian Society of Hypertension.

My academic activity also involved contributions to the elaboration of textbooks and books for the medical educational process. I've contributed to more than twenty textbooks and manuals for medical students and physicians, as an editor or author, in the post-doctoral period, and author of 53 book chapters. I want to mention here some of the most representative textbooks and manuals:

- 2022: *Internal medicine. Cardiovascular, respiratory and blood diseases*, 679 p. **Editors:** L. Șorodoc, **Cătălina Lionte**, Victoriția Șorodoc, C. Stătescu, RA Sascău. Iași: Ed. Gr. T. Popa 2022. ISBN 978-606-544-806-3.
- 2021: *Medicina internă de la caz la caz*, 282 p. Ed. Coord. Prof. dr. Laurențiu Șorodoc. Authors (alphabetical order): Iulia Gabriela Adascaliței, … **Cătălina Lionte**, …, Alexandra Simona Zamfir. Iași: PIM 2021. ISBN 978-606-13-6008-6.
- 2019: *Medicina internă, patologie respiratorie, cardiovasculară și hematologică*, 857 p. Eds. Laurentiu Șorodoc (coord), Antoniu Octavian Petriș, Cristian Statescu, Ciprian Rezuș, Ioana Dana Alexa. Authors (alphabetical order): Ștefan Ailoaiei, …, **Cătălina Lionte**, …, Luminita Gina Vâță. Iași: Sedcom Libris 2019. ISBN 978-973-670-589-2.
- 2018: *Toxicologie practică*, 180 p. Chief Ed: Prof. dr. L. Șorodoc. Authors: L. Șorodoc, **Cătălina Lionte**, …, M. Constantin. Iași: PIM 2018. ISBN 978-606-13-4664-6.
- 2014 : *Compendiu de medicină internă*, 634 p. Ed : Cătălina Arsenescu Georgescu. Authors (alphabetical order): Cătălina Arsenescu Georgescu, …, **Cătălina Lionte**, ... Daniela Maria Tănase. Iași : Ed. Gr. T. Popa 2014. ISBN 978-606-544-287-0.
- 2014: *Terapeutica medicală, 3rd Ed*, 885 p. Eds: Gabriel Ungureanu, Adrian Covic. Authors (alphabetical order): Ioana Dana Alexa, …, **Cătălina Lionte**, …, Carmen Vulpoi. Iași: Polirom 2014. ISBN print 978-973-46-4804-7.
- 2013: *Clinical Toxicology. A comprehensive Guide*. 363 p. **Editor: Cătălina Lionte**. 'Gr.T.Popa' Publisher, U.M.F. Iași. ISBN: 978-606-544-166-8.
- 2013: *La Toxicologie Pratique*, 207 p. Coordinateur(ed): Maître de conférences dr. Laurentiu Șorodoc. Authors: Laurentiu Șorodoc, **Cătălina Lionte**, Ovidiu Petriș, Cristina Bologa,Victoriția Șorodoc, Gabriela Puha, Eugen Neculai Gazzi. Maison d'édition ,,Gr.T.Popa", U.M.F. Iași. ISBN: 978-606-544-165-1.
- 2009: *Toxicologie clinică de urgență, vol II. Intoxicații nemedicamentoase*, 397 p. Authors: Laurentiu Șorodoc (editor), **Cătălina Lionte**, Ovidiu Rusalim Petriș, Victoriția Șorodoc. Iași: Editura JUNIMEA, 2009. ISBN: 973-37-1023-7, vol 2. ISBN: 978-973-37-1409-5.
- 2005: *Toxicologie clinică de urgență, vol I*, 350 p. Authors: Laurentiu Șorodoc (ed), **Cătălina Lionte**, Mihai Frasin, Radu Andrei, Victoriția Simionescu, Ovidiu Petriș. Iași: Editura JUNIMEA, 2005. ISBN: 973-37- 1023-7, vol 1 ISBN: 973-3710000-8.
- 2004: *Hipoglicemiile în practica medicală și toxicologică,* 308 p. Author: **Cătălina Lionte**, Iași: Editura Junimea, 2004, colecția Esculap, nr.101. ISBN 973-37-0939-5.

Between November 2020 – January 2021, I acted as an external expert on behalf of SIVECO ROMANIA, on the curricula analysis of the Project POCU 122555 – "*Innovative solutions for Universities and Technical college to ensure competitivity of the educational process in correlation with domains of intelligent specialties - SUCCES"*, code MySMIS 122555/2018. Project director was Assoc. Prof. Dr. Irina Costache.

Scientific activity

My scientific research began as soon as I stepped into university life and has been ongoing ever since. As a result of the improvement in my research skills, over the years I have

managed to publish original review articles as first author or co-author. In the early years of my career, I have published several articles in B and B+ Romanian journals or conference and congress proceedings.

The opportunity to familiarize myself with the requirements of article writing and publication criteria arose when I was invited as a peer reviewer for ISI journals: Human and Experimental Toxicology, and Basic and Clinical Pharmacology and Toxicology.

I have completed my PhD thesis, entitled**" Hypoglycemia in acute exogenous poisoning which affect liver"**, under the coordination of late Professor Jan Hurjui, MD, PhD and I publicly presented its final results in 2002. The above-mentioned PhD thesis approached interdisciplinary issues in the areas of internal medicine, clinical toxicology, diabetology and pharmacology, namely hypoglycemia induced in both diabetic and non-diabetic patients with acute exposures to drugs and non-pharmaceutical agents which act on glucose metabolism and which may induce hypoglycemia through severe acute liver failure. My PhD research performed the assessment of the prevalence and characteristics of acute poisoning in Iasi County, with a focus on acute poisonings which induce hypoglycemia. Another important part of the research was the study of the experimental acute poisoning with acetaminophen, and the synthesis and characterization of two original methionine derivatives, which were used as antidotes for this poisoning, with promising results, that will encourage future research to demonstrate their potential for use in humans.

In the years after the completion of my PhD thesis, my research interests have progressively widened. First, I've continued to be involved in fundamental research as part of the multidisciplinary team I collaborated with for my PhD thesis, for developing and characterization of new molecules based on essential amino-acids, such as methionine, with potential to be used as drugs in different areas of pathology. The results of these researches were published in ISI journals, and received several UEFISCDI awards.

Another research direction I've followed focused on the effects of therapeutical and overdose involving drugs and acute exposure to non-pharmaceutical agents, with a preoccupation for rhabdomyolysis, cardiovascular effects, metabolic consequences and life-threatening complications in these situations. Over the years, I was interested in the role of biomarkers and multimodality imaging in the early diagnosis and the outcome prediction of the patients admitted with medical emergencies, such as acute poisoning, heart failure, and recently, SARS-COV2 infection. A special interest was the role of echocardiography in the assessment of acute poisoning. Another direction of my scientific development was the role of the modern therapies in the management of acutely poisoned patients. Last but not least, I am continuously expressing a special interest in the field of risk assessment in medical patients, using statistical developed methods, such as the nomograms.

I have published the results of my scientific research activity in Web of Science Core Collection indexed articles, as well as in papers belonging to other international databases. I have also disseminated my scientific results at local, national and international congresses, as well as various conferences, seminars or workshops. Up until now, the results of my scientific research activity have formed the basis for 50 research papers rated by Clarivate Analytics Web of Science Core Collection, 35 papers indexed by other international databases, other 23 papers in various publications, 7 abstracts rated by Clarivate Analytics Web of Science Core Collection and 24 other abstracts. These articles have drawn a total of 189 citations in Clarivate Analytics Web of Science Core Collection publications, with a H-index of 10, and 592 citations in Google Scholar, with a h-index of 15. I have also contributed with oral presentations and posters to multiple international and national congresses or conferences.

I was part of the teams of 2 different research projects won in competition:

- Internal research grant of the "Grigore T. Popa" University of Medicine and Pharmacy, Iași, 2015-2016: *Development and validation of an original nomogram using biomarkers, clinical, ECG and echocardiogram data for early in-hospital course and outcome prediction in acute poisoning with systemic toxins* – **project director** – financing contract no. 30884/30.12.2014.
- Internal research grant of the "Grigore T. Popa" University of Medicine and Pharmacy, Iași, 2009-2010: *Optimization of the antidote therapy in acute poisoning with organophosphates pesticides through the development of an original in vitro method for testing reactivity of cholinesterase* – **team member** – project director Prof. Laurențiu Șorodoc, MD, PhD.

I also took part, as a co-investigator, in 5 national clinical studies, one phase III international clinical study (*Effects of ivabradine in patients with stable coronary artery disease without clinical heart failure* - **SIGNIFY**) and one international observational study (*Non-interventional Study Describing Patients´ Perception on Anticoagulant Treatment and Treatment Convenience When Treated With Pradaxa or Vitamine K Antagonist for Stroke Prevention in Non-Valvular Atrial Fibrillation* - **RE–SONANCE NIS**). My active involvement in these research projects was useful for the development of teamwork skills and discipline needed to coordinate and finalize them.

For my professional and scientific activity, I've received several awards through the years:

- UEFISCDI – 2021 Competition – Rewarding research results – PN-III-P1-1.1-PRECISI-2021- 64350: "Biomarkers of Inflammation and Inflammation-Related Indexes upon Emergency Department Admission Are Predictive for the Risk of Intensive Care Unit Hospitalization and Mortality in Acute Poisoning: A 6-Year Prospective Observational Study".
- UEFISCDI – 2021 Competition – Rewarding research results – PN-III-P1-1.1-PRECISI-2021- 64347: "First Case of Acute Poisoning with Amiodarone and Flecainide in Attempted Suicide Successfully Managed with Lipid Emulsion Therapy in the Emergency Department: Case Report and Literature Review".
- UEFISCDI – 2021 Competition – Rewarding research results – PN-III-P1-1.1-PRECISI-2021- 64344: "Association of Multiple Glycemic Parameters at Hospital Admission with Mortality and Short-Term Outcomes in Acutely Poisoned Patients".
- UEFISCDI – 2021 Competition – Rewarding research results – PN-III-P1-1.1-PRECISI-2021-61965: "Immobilization and release studies of triazole derivatives from grafted copolymer based on gellan-carrying betaine units"
- UEFISCDI – 2017 Competition – Rewarding research results – PN-III-P1-1.1-PRECISI-2017-18049: "Usefulness of Transthoracic Echocardiography Parameters and Brain Natriuretic Peptide as Mortality Predictors in Hospitalized Acutely Poisoned Patients: A Prospective Observational Study".
- UEFISCDI – 2017 Competition – Rewarding research results – PN-III-P1-1.1-PRECISI-2017-18047: "Development and validation of a risk-prediction nomogram for in-hospital mortality in adults poisoned with drugs and nonpharmaceutical agents - an observational study".
- UEFISCDI – 2013 Competition – Rewarding research results – PN-II-RU-PRECISI-2013- 7-3302: "Synthesis and antimicrobial activity of new amidic derivatives of 5-nitroindazol-1-yl acetic acid encapsulated into alginate/pectin particles".

- UEFISCDI – 2013 Competition – Rewarding research results – PN-II-RU-PRECISI-2013- 7-3783: "Optimization reaction for obtaining some n-[p-(r)-benzoyl]-l-glutamine derivatives with pharmaceutical action".
- UEFISCDI – 2012 Competition – Rewarding research results – PN-II-RU-PRECISI-2012-6-1264: "Double crosslinked chitosan and gelatin submicronic capsules entrapping amino acid derivatives with potential antitumoral activity".

In conclusion to this overview of my activity, I believe it is important to highlight my contributions as:

- investigator in clinical trials with international participation and research grants obtained by competition (1 as project manager, 4 as a team member);
- participation in original clinical collaborative researches, with the publication of research results in journals indexed by Thomson ISI Web of Science Core Collection and presentation of papers at European congresses;
- author of one chapter published in international textbooks and editor/co-author of manuals of internal medicine and clinical toxicology for students and young physicians in Romanian, English and French;
- participation in continuing education and educational courses;
- publication of articles indexed and rated in international databases which achieved 189 citations in Clarivate Analytics Web of Science Core Collection publications, with a **Hirsch-index of 10**.
- 9 award-winning ISI articles in competitions organized by UEFISCDI.

SECTION I

POSTDOCTORAL SCIENTIFIC ACHIEVEMENTS

I. THE ROLE OF BIOMARKERS AND MULTIMODALITY IMAGING IN THE EARLY DIAGNOSIS AND OUTCOME PREDICTION FOR PATIENTS ADMITTED IN INTERNAL MEDICINE DEPARTMENT

I.1. Traditional and new biomarkers useful for outcome prediction

This direction of research is reflected in the following published articles:

1. **Lionte, C,** Bologa, C, Agafiti, I, Sorodoc, V, Petris, OR, Jaba, E, Sorodoc, L. Association of Multiple Glycemic Parameters at Hospital Admission with Mortality and Short-Term Outcomes in Acutely Poisoned Patients. *Diagnostics* 2021; 11 (2): article number 361. DOI 10.3390/diagnostics11020361 **(IF 3.706)**
2. **Lionte, C;** Bologa, C; Sorodoc, V; Petris, OR; Puha, G; Stoica, A; Ceasovschih, A; Jaba, E; Sorodoc, L. Biomarkers of Inflammation and Inflammation-Related Indexes upon Emergency Department Admission Are Predictive for the Risk of Intensive Care Unit Hospitalization and Mortality in Acute Poisoning: A 6-Year Prospective Observational Study. *Disease Markers* Vol 2021 Article Number 4696156 DOI 10.1155/2021/4696156 (**IF 3.434**)
3. **Lionte, C,** Sorodoc, V, Tuchilus, C, Cimpoiesu, D, Jaba, E. Biomarkers, lactate, and clinical scores as outcome predictors in systemic poisons exposures. *Hum & Exp Toxicol* 2017; 36 (7): 651-662. (**IF 1.840**)
4. Stoica, A; Sorodoc, V; **Lionte, C**; Jaba, IM; Costache, I; Anisie, E; Tuchilus, C; Petris, OR; Sirbu, O; Jaba, E; Ceasovschih, A; Vata, L; Sorodoc, L. Acute cardiac dyspnea in the emergency department: diagnostic value of N-terminal prohormone of brain natriuretic peptide and galectin-3. *Journal of International Medical Research* 2019; 47 (1):159-172. **(IF 1.287)**
5. AD Diaconu, I Ostafie, A Ceasovschih, V Șorodoc, **C Lionte**, C Ancuța, L Șorodoc (**All authors contributed equally to this work**). Role of Vitamin D in Systemic Sclerosis: A Systematic Literature Review. *Journal of Immunology Research*, vol. 2021, Article ID 9782994, 15 pages, 2021. https://doi.org/10.1155/2021/9782994 (**IF 4.818**)

Background

Working in an Emergency Hospital, our main focus represented the management of patients with medical emergencies presented to Emergency Department (ED) and admitted in the Internal Medicine Department. As a result, patients admitted for acute poisoning and acute dyspnea as consequence of respiratory or heart failure were the majority of patients admitted to our department, and an important part of our research domains.

Acute poisonings represent an important cause of mortality and a challenge to the ED in many countries. The majority of cases presented to the ED are self-poisonings, and the substances which have been causing severe outcomes for the past decade are antidepressants, stimulants and street drugs, antihistamines, and anticonvulsants (Gummin et al., 2019). Nevertheless, acute toxicities after pesticide exposure globally account for the overwhelming majority of poisoning deaths (Senarathna et al., 2012). Up to 40% of the patients visiting the ED with an intoxication are admitted to the hospital, and an average of 1.5–3.7% poisoned patients need intensive care unit (ICU) admission (Brandenburg et al., 2017).

The poisoning severity score (PSS), developed by the International Programme on Chemical Safety, the Commission of the European Union, and the European Association of Poison Centers and Clinical Toxicologists, proved to have a prospective value in some acute poisoning, in correlation with other clinical scales, or electrocardiogram (ECG) parameters (Casey et al., 1998; Akdur et al., 2010).

General approach of a poisoned patient uses both routine laboratory tests and, in some circumstances, specific biomarkers developed for cardiac emergencies (troponins, cardiac enzymes, and natriuretic peptides). Thus far, some investigators have used several laboratory tests as prognostic indicators to identify high-risk patients in acetaminophen, CO, or paraquat poisoning (Shah et al., 2011; Kao et al., 2009; Liu et al., 2013). Also, the prognostic utility of serum lactate to predict drug-overdose fatality was addressed retrospectively (Manini et al., 2010). ECG parameters, especially the QTc interval, proved to have a role in predicting morbidity and mortality in organophosphate pesticide, herbicide poisoning, and in antipsychotic drugs poisoning (Kim et al, 2014; Akdur et al., 2010; Berling & Isbister, 2015).

Hyper- and hypoglycemia are a common problem in hospitalized patients with or without a history of diabetes mellitus (DM), (Boord et al., 2009; Zaccardi et al., 2018). Hyperglycemia proved to be associated with increased morbidity, mortality and poor outcomes in patients with an acute illness, such as coronary syndromes, pneumonia, or exacerbation of a chronic obstructive pulmonary disease (Garadah et al., 2009; Foltran et al., 2013; Baker et al., 2007). Hyperglycemia might exert an even more deleterious effect on those patients without DM than among patients with DM during acute illness (Krinsley, 2009). Increased glucose variability was associated with longer hospitalization and mortality in both nondiabetic and diabetic patients, as well as with in-hospital complications following surgery (Akirov et al., 2017; Shohat et al., 2018). Hyperglycemia is not a common feature of overdose (Jones, 2016). There is a wide range of studies about hyperglycemia in both medical, surgical, and ICU patients (Hermanides et al., 2010; Li et al., 2019; Meynaar et al., 2012; Dungan et al., 2011).

Appropriate risk stratification using biomarkers of inflammation and inflammation-related indexes based on peripheral complete blood cell (CBC) counts measured in the ED for the need of ICU hospitalization and in-hospital mortality remains a challenge in poisoning with both pharmaceutical and nonpharmaceutical agents. On many occasions, patients are brought in the ED with an altered mental status after being exposed to a xenobiotic, and it is difficult to make a quick prognosis assessment, especially when a toxicological screen or a quantitative measurement of the poison involved is not available or is delayed. High sensitivity C-reactive protein (CRP), CBC, and inflammation-related indexes based on CBC are readily available in the ED and inexpensive, but no studies have evaluated the prognostic value of these parameters in patients admitted to the hospital with acute poisonings with undifferentiated toxins.

The large spectrum of subjective symptoms such as dyspnea, palpitations, and chest pain often make the clinical diagnosis of acute heart failure (AHF) misleading. In emergency settings, patients can overestimate their symptoms because of panic and anxiety; additionally, life-threatening conditions may have an indolent presentation. Population categories at risk of misdiagnosis are young adults with less specific clinical manifestations and patients with comorbidities or chronic treatment for heart failure; such conditions lead to difficult estimation of physical examination findings. Noninvasive paraclinical investigations such as standard 12-lead ECG and chest radiography are needed for further assessment. In most cases, these techniques provide sufficient information to determine a cardiac etiology. Nevertheless, transthoracic echocardiography (TTE) is indispensable for proper evaluation of patients suspected to have acute heart failure, but it is often unavailable in the ED and is highly operator-dependent. Approximately 64% to 78% of patients with AHF are admitted through the ED portal (Searle et al., 2016; Logeart et al., 2013; Fonarow et al., 2004). Premature ED discharge

of a patient with acute or decompensated heart failure can have severe consequences. The assessment of patients with acute heart failure in the ED is burdened by the increased number of presentations, prolonged waiting time, and deficit of medical staff. Even when facing non-urgent and possible avoidable ED services, the progressive tendency toward defensive medicine and the continuous increase in patients' expectations and demands necessitate objective methods of evaluation before discharge. Biomarkers are strongly objective when making medical decisions. The diagnostic and prognostic performance of natriuretic peptides [brain natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP)] when assessing patients with heart failure has achieved worldwide agreement. The main limitation of these biomarkers is the different cutoff values established for the acute and chronic manifestations of heart failure. Additionally, parameters such as age, sex, body mass index (BMI), high-output states (e.g., cirrhosis, sepsis), and renal function interfere with their diagnostic abilities. Novel therapies in acute heart failure (e.g., neutral endopeptidase inhibitors) even further modify the natriuretic peptide levels, creating a divergent pattern: increased levels of BNP and decreased levels of NTproBNP (Yancy et al., 2017; Stokes et al., 2016; Wettersten & Maisel, 2016). Several biomarkers, that reflect different pathophysiological mechanisms, have been proposed for the diagnosis, prognosis, and risk stratification of patients with acute heart failure when natriuretic peptide levels are inconclusive. Galectin-3, a member of the lectin family, is secreted by activated macrophages and is involved in biological processes such as inflammation, cardiac remodeling, and myofibroblast proliferation. Galectin-3 was recently approved by the Food and Drug Administration for its prognosis utility in acute heart failure, fulfilling important criteria that make it a possible ideal biomarker: early recognition of hypertrophic and fibrotic cardiac injuries, risk stratification, and potential therapeutic target as proven by experimental studies (Song et al., 2015; AbouEzzeddine et al, 2015; Wettersten & Maisel, 2016).

Low levels of vitamin D can increase the likelihood of developing multiple acute and chronic ailments including cardiovascular and autoimmune diseases, diabetes, cancer, infectious diseases, dental caries and periodontal disease. Vitamin D deficiency is significantly associated with increased risk for COVID-19 (Katz et al., 2021).

The role of vitamin D in cardioprotection is widely accepted, although its mechanisms are still poorly understood. It seems that vitamin D acts via the renin system to decrease blood pressure, increase vascular endothelial growth factor, and decrease the production of endothelium derived contracting factors (Umar et al., 2008).

Because of the pleiotropic roles of vitamin D, including its immunomodulatory, cardioprotective, and antifibrotic properties, suboptimal vitamin D could interfere with major pathobiological pathways in inflammatory and autoimmune diseases. Thus, we summarized in a review the role of vitamin D in systemic sclerosis.

Study on biomarkers and lactate as outcome predictors in intoxication with systemic poisons

There is little information of the role of arterial lactate measurement and other routine laboratory tests or cardiac biomarkers in the risk assessment and prognosis after acute exposure to different types of systemic poisons (drugs, chemicals, gases, or plant toxins). To the best of our knowledge, no data regarding markers of poor prognosis and death suitable for all types of systemic poisons exposures are available in literature.

Aim of the study

Our aim was to analyze the potential role of several conventional laboratory tests, biomarkers, and ECG parameters, in correlation with clinical scores, for early prediction of the

need for ICU therapy, complications, short-term outcomes, and mortality in patients intoxicated with various systemic poisons, irrespective of dose or route of exposure. These parameters could be used immediately after admission, in order to identify patients at risk of a poor outcome or death, thus the management of these patients can be optimally adjusted.

Materials and methods

Study design and setting

This work was designed as a prospective, cohort study in a tertiary referral center for toxicology, admitting patients with acute poisoning from Romania. Over a period of 9 months (April 2015 to December 2015), we enrolled consecutive patients who were addressed to the hospital with acute poisoning diagnosed after exposure to a systemic poison. All subjects or their family (in the situation of an unconscious patient) signed an informed consent prior to enrollment. The study was funded by an internal research grant of the university and approved by the Ethics Committee of the university and hospital (no. 52/05.01.2015 and no. 7321/11.02.2015, respectively).

Selection of participants

The study included consecutive patients acutely exposed to systemic poisons that were referred to the ED and admitted to a medical clinic or ICU, older than 18 years, irrespective of gender. Patients were poisoned with prescription drugs (e.g., sedative-hypnotics, antidepressants, anticonvulsants, and cardiac medications), over-the-counter medicines – OTCs (e.g., salicylates, acetaminophen, non-steroidal anti-inflammatory drugs – NSAIDs, etc.), and illicit drugs (cocaine, amphetamines, opiates, cannabis, etc.), also with non-pharmaceutical agents such as pesticides, toxic gases (e.g., CO), toxic alcohols (e.g., methanol and ethylene glycol), and plant toxins (e.g., wild mushrooms), or were exposed to multiple systemic poisons.

Patients without a signed informed consent, younger than 18 years, with a documented history of diabetes, chronic kidney disease, respiratory failure, or cardiovascular disease, with caustic poisoning, and with an acute pathology associated to poisoning (i.e., trauma, burns, etc.), or pronounced dead in the ED were excluded from our study.

Clinical and laboratory assessment

All patients who arrived in the ED after exposure to a systemic poison, diagnosed with acute poisoning after anamnesis, clinical examination, and toxicological tests (serum toxicology for ethanol, digitalis, cholinesterase, COHb level, and urine toxicology screens which included acetaminophen, salicylates, amphetamines, methamphetamines, opiates, benzodiazepines, cocaine, barbiturates, phencyclidine, tetrahydrocannabinol, and tricyclic antidepressants), underwent routine assessment in the ED: CBC, arterial lactate, glucose, electrolytes, CRP, troponin I (TnI), BNP, CK, MB isoenzyme of creatine kinase (CKMB), myoglobin, and renal and liver function profile. Selected poison concentrations were assessed the next day from the initial serum sample using gas chromatography-mass spectrometry techniques, if there was no available toxicological exam upon admission in the ED.

PSS was determined in all patients taking into account only the clinical symptoms and signs observed and not based on parameters such as amounts ingested or serum/plasma concentrations. We used the grading system described by Persson et al.: (1) minor poisoning: mild, transient, and spontaneously resolving symptoms; (2) moderate poisoning: pronounced or prolonged symptoms; (3) severe poisoning: severe or life-threatening symptoms; and (4) fatal poisoning: death on arrival in ED (Persson et al., 1998).

A 12-lead ECG (to determine rhythm, ST-T changes, and PR and QTc intervals) was recorded in the ED upon presentation. All included patients were subjected to clinical and ECG monitoring, pulse oximetry, and non-invasive blood pressure measurements. Blood samples for arterial lactate, TnI, BNP, and CKMB analysis were collected upon presentation (0 h) and thereafter at the discretion of the attending physician, but mainly 4 h (lactate), respectively, 6 h from presentation (TnI, CKMB, NT-proBNP), in order to assess myocardial injury (Roffi et al., 2015; Thygesen et al., 2012). The blood and urine samples were analyzed using ABL 90 (Radiometer, Denmark) and GEM PREMIER 3500 (Instrumentation Laboratory, Bedford, Massachusetts, USA), Triage1Meter Pro TOX Drug Screen (Alere, Waltham, Massachusetts, USA), PATHFAST1 Cardiac Biomarker Analyzer (LSI Medience Corporation, Japan), Sysmex XT-4000i-Automated Hematology Analyzer (Sysmex Corporation, Japan), and ARCHITECT c16000 clinical chemistry analyzer (Abbott Laboratories, Abbott Park, Illinois, USA). According to the manufacturer, the range of normal values for arterial lactate concentration is 0.3–0.8 mmol/L, for CKMB is 0–4.3 ng/mL, or 2–25 U/L, and for TnI is 0–0.02 ng/mL. For BNP and NT-proBNP levels, we used the cutoff limit of <100 pg/mL and <300 pg/mL, respectively, according to the guidelines (McMurray et al., 2012). The QTc was calculated using the Bazett formula and was considered prolonged if greater than 0.44 s (Chan et al., 2007). An internal medicine specialist and a cardiologist conducted the QT interval measurements, with no statistical differences between readings.

The main outcome measure was status at hospital discharge. A favorable short-term outcome was considered in the absence of morbidity, or the presence of a complication affecting only one organ or system resolved during hospitalization. A poor short-term outcome was defined as in-hospital multiple complications or death. Early complications were defined as follows: rhabdomyolysis (CK > 1000 IU/L); acute respiratory failure, defined as a condition requiring mechanical ventilation for correction of hypoxia, or hypercapnia, for more than 24 h; cardiovascular complications: hypotension, defined as systolic blood pressure (SBP) less than 90 mmHg, dysrhythmias with circulatory compromise, and acute myocardial injury (based on cardiac biomarkers and ECG); acute liver injury, defined as markedly elevated serum alanine and aspartate aminotransferase levels >10 times the upper limit of the normal range, accompanied by mild or moderate elevations in alkaline phosphatase levels (Chalasani et al., 2014); acute kidney injury, defined as urine volume <0.5 mL/kg/h for 6 h, based on Kidney Disease: Improving Global Outcomes criteria (KDIGO, 2012); and multiple complications (at least two organs or systems affected).

Statistical analysis

Data are presented as mean ± standard deviation, median with interquartile range, or frequency. Student's t-test or Mann–Whitney U test for normal distributed variables as well as the χ^2 test and Cochrane's statistic for categorical variables were used to perform univariate analysis. A p value < 0.05 was considered statistically significant. First, we applied simple binary logistic regression for each statistically significant variable. Then, we applied multivariate logistic regression on clusters of variables, which assess the systems and organs. Risk was expressed as odds ratios (OR) with confidence intervals (CI). Goodness-of-fit for multivariate models was confirmed using Hosmer and Lemeshow test. The receiver operating characteristic (ROC) methodology was used to analyze the discriminatory capacity of predictive variables. ROC analyses were expressed as curve plots and calculated area under the curve (AUC) with 95% CI, the associated p value representing the likelihood of the null hypothesis (AUC = 0.5). Statistical analyses were performed with SPSS (version 22.0; SPSS, Inc., Chicago, Illinois, USA).

Results

During the study period, 174 patients were admitted into the hospital after exposure to a systemic poison and 120 patients were enrolled in this study (Figure I.1).

The mean age of the patients included was 42.32 ± 16.88 years (range, 18–83 years). The time interval between acute poison exposure and presentation to ED ranged 0.5–4.5 h. The patients were categorized into groups according to their need for ICU therapy, morbidity, outcome, and survival. The population's clinical, ECG, and laboratory characteristics are described in Table I.1. Poisons involved (Table I.2) were mainly represented by combination of toxins (30%), which included ethanol co-ingestion with antidepressants, benzodiazepines, barbiturates, antipsychotics, and prescription drugs (i.e., sedative-hypnotics – 15%, antidepressants, antipsychotics and antiepileptics – 12.9% and cardiovascular drugs – 2.5%).

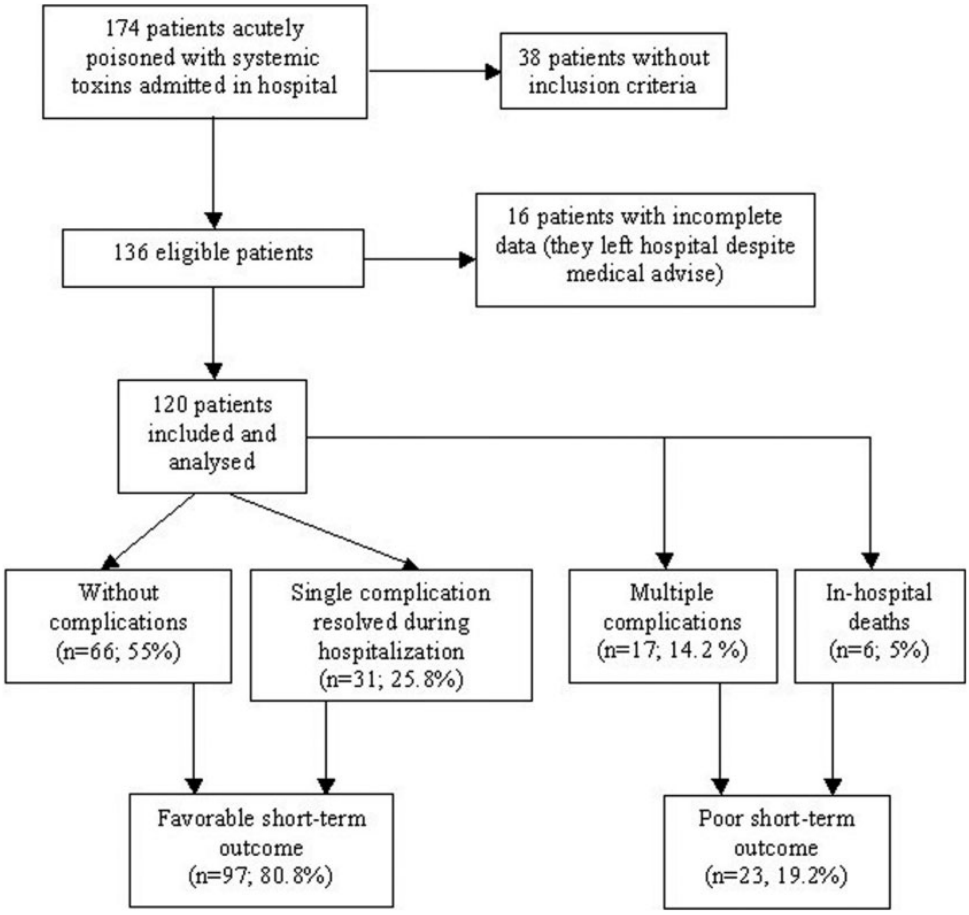


Figure I.1. Flowchart of patients included in the study, their complications and outcomes

Nonpharmaceutical agents involved (Table I.2) were pesticides (12.5%), followed by toxic gases (6.66%), toxic alcohols, and chemicals (5%). The majority of cases (92.5%) were self-poisonings, while nine cases (7.5%) were accidental poison exposures. Among the population studied, 84 patients (70%) had a positive toxicological exam on admission. For the rest of the 36 patients, there was no available technique to evidence the poison in ED, the diagnosis was made based on history of exposure, clinical and laboratory data, and confirmed the next day by serum quantitation using special techniques. The outcome was favorable in 66 patients (55%), 23 patients experienced a poor short-term outcome (19.2%), and 21 patients needed ICU admission (17.5%). Complications occurred in 54 cases (45%). About 17.5% of

patients developed multiple complications, which included myocardial damage. Cardiovascular complications alone were encountered in 8.33% of the patients.

Table I.1. Patients' demographics, clinical, ECG, and laboratory parameters based on observed short-term outcomes.

Patients characteristics	Favorable short-term outcome ($N = 97$)	Poor short-term outcome ($N = 23$)	p Value
Demographic characteristics			
Age (years)	40.26 ± 16.23	51.04 ± 17.14	0.005
Males/females, *n* (%)	44/53 (75.9/85.5)	14/9 (24.1/14.5)	0.134
Clinical data			
PSS, *n* (%)			
Minor	44 (45.4)	0	0.001
Moderate	45 (46.4)	3 (13)	
Severe	8 (8.2)	20 (87)	
GCS, *n* (%)			
<10	10 (10.3)	15 (65.2)	0.001
≥10	87 (89.7)	8 (34.8)	
HR (b/min)	88.36 ± 21.31	106.22 ± 31.28	0.001
SBP (mmHg)	123.63 ± 23.99	120.57 ± 36.09	0.621
DBP (mmHg)	76.08 ± 13.67	72.61 ± 19.38	0.317
ECG parameter			
QTc interval (ms)	411.12 ± 77.43	393.86 ± 143.70	0.427
Laboratory tests upon ED arrival			
Ethanol co-ingestion (mg/dL)	49.44 ± 107.13	37.64 ± 83.03	0.623
Initial lactate (mmol/L)	1.87 ± 1.33	6.04 ± 4.16	0.001
pH	7.40 ± 0.07	7.23 ± 0.21	0.001
HCO_3 (mmol/L)	24.14 ± 2.86	18.12 ± 7.30	0.001
CRP (mg/dL)	1.09 ± 3.74	3.84 ± 5.43	0.005
RDW (%)	13.39 ± 1.25	14.16 ± 1.36	0.042
WBC (×1000/mcgL)	8.63 ± 3.02	15.39 ± 6.14	0.001
Initial TnI (ng/mL)	0.04 ± 0.10	0.14 ± 0.38	0.02
BNP (pg/mL)	38.21 ± 78.18	225.14 ± 205.58	0.001
Initial CKMB (ng/mL)	6.67 ± 10.09	19.02 ± 24.87	0.001
Biomarkers' follow-up			
4h-Lactate (mmol/L)	2.2 ± 1.02	5.83 ± 4.57	0.001
6h-TnI (ng/mL)	0.02 ± 0.13	0.27 ± 0.67	0.001
6h-CKMB (U/L)	20.81 ± 9.1	101.61 ± 207.74	0.001
6h-NTproBNP (pg/mL)	122.66 ± 164.13	2430.22 ± 4510.12	0.001

PSS: poisoning severity score; GCS: Glasgow Coma Scale; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; CRP: C-reactive protein; RDW: red cell distribution width; WBC: white blood cells; 6h-TnI: troponin I level 6 h after arrival to ED; ED: emergency department; CKMB: MB isoenzyme of creatine kinase; 6h-CKMB: MB isoenzyme of creatine kinase level 6 h after ED admission; BNP: brain natriuretic peptide; 6h-NT-proBNP: N-terminal pro-B-type natriuretic peptide level 6 h after emergency department admission.

Complications were recorded mainly in poisoning with toxic alcohols (80%), pesticides (53.3%), antidepressants (46.2%), and combinations of toxins (38.9%). Within toxin category, patients in need for ICU therapy were those poisoned with toxic alcohols (80%), combination of poisons (22.2%), prescription drugs (20%), and toxic gases (12.5%).

The hospitalization was significantly prolonged in patients with a severe PSS on admission (6.39 ± 5.62 days; $p < 0.001$) and in patients who developed complications as a result of the poisoning (5.43 ± 4.46 days vs. 3.2 ± 1.76 days; $p < 0.001$). Out of the 120 patients included, 6 patients died during hospitalization (5%) as a cause of multi-organ failure, having a length of hospital stay of 4 ± 3.22 days, non-significantly different from the survivors. Deaths were recorded in patients exposed to toxic alcohols and combination of poisons (two cases each), pesticides and antidepressants (one case each).

Table I.2. Distribution of poison exposures based on short term-outcomes and mortality recorded.

Toxin category	Favorable short-term outcome *N* (%)[a]	Poor short-term outcome *N* (%)[a]	Deaths *N* (%)[a]	Total *N* (%)[b]
Combination of poisons	30 (83.3)	6 (16.7)	2 (5.55)	36 (30)
Prescription drugs (antidepressants, antiepileptics, antipsychotics, antidemential, antiparasitic, and antimicrobials, cardiovascular medicines, sedative-hypnotics, tuberculostatic agents)	29 (80.55)	7 (19.45)	1 (2.78)	36 (30)
Pesticides	12 (78.6)	3 (21.4)	1 (6.67)	15 (12.5)
OTCs (acetaminophen, NSAIDs, salicylates)	11 (91.67)	1 (8.33)	0	12 (10)
Toxic gases	6 (75)	2 (25)	0	8 (6.66)
Drugs of abuse (including opiates)	7 (100)	0	0	7 (5.83)
Toxic alcohols and chemicals (methanol, ethyleneglycol, solvents, formaldehyde)	2 (20)	4 (80)	2 (20)	6 (5)
Plant toxins (wild mushrooms)	1 (100)	0	0	1 (0.01)
Total cases	97 (80.8)	23 (19.2)	6 (5)	120

OTCs: over-the-counter drugs; NSAID: nonsteroidal anti-inflammatory drug. [a] Within toxin category. [b] Within entire cohort studied.

Distribution of variables within complication/no complication groups and survivors/non-survivors is presented in Table I.3.

Table I.3. Patients' characteristics in correlation with occurrence of complications and mortality.

Patient characteristics	Complications groups			Mortality groups		
	No complications ($N = 66$)	With complications ($N = 54$)	*p* Value	Survivors ($n = 114$)	Deaths ($n = 6$)	*p* Value
Age	38.98 ± 14.80	46.39 ± 18.48	0.016	41.2 ± 16.52	63.5 ± 7.53	0.001
Males/females, *n* (%)	24/42 (36.4/63.6)	34/20 (63/37)	0.006	56/58 (96.6/93.5)	2/4 (3.4/6.5)	0.451
GCS, *n* (%)						
<10	3 (4.5)	22 (40.7)	0.001	21 (84)	4 (16)	0.017
≥10	63 (95.5)	32 (59.3)		93 (97.9)	2 (2.1)	
Initial lactate (mmol/L)	1.78 ± 1.07	3.69 ± 3.62	0.001	2.35 ± 2.16	8.28 ± 5.49	0.001
4h-Lactate (mmol/L)	2.17 ± 0.98	3.60 ± 3.59	0.002	2.45 ± 1.3	11.21 ± 5.96	0.001
pH	7.41 ± 0.06	7.32 ± 0.17	0.001	7.38 ± 0.09	7.07 ± 0.28	0.001
HCO3 (mmol/L)	24.21 ± 2.58	21.48 ± 6.1	0.001	23.52 ± 3.8	12.68 ± 8.06	0.001
CRP (mg/dL)	0.61 ± 1.51	2.84 ± 5.88	0.004	1.61 ± 4.33	1.66 ± 1.4	0.978
RDW (%)	13.43 ± 1.39	13.58 ± 1.21	0.554	13.44 ± 1.28	14.65 ± 1.37	0.028
WBC (×1000/mcgL)	8.21 ± 2.5	12.01 ± 5.68	0.001	9.63 ± 4.51	15.48 ± 3.3	0.002
Initial BNP (pg/mL)	21.13 ± 25.12	119.41 ± 184.92	0.001	53.91 ± 123.68	282.74 ± 150.51	0.001
6h-NT-proBNP (pg/mL)	97.08 ± 139.7	1136.77 ± 3119.37	0.008	367.22 ± 1715.82	4321.67 ± 5045.41	0.001
Initial TnI (ng/mL)	0.043 ± 0.121	0.077 ± 0.25	0.323	0.06 ± 0.195	0.027 ± 0.019	0.68
6h-TnI (ng/mL)	0.029 ± 0.156	0.122 ± 0.452	0.124	0.06 ± 0.3	0.292 ± 0.637	0.088
Initial CKMB (ng/mL)	5.27 ± 8.65	13.62 ± 19.07	0.002	8.67 ± 14.15	15.77 ± 25.68	0.255
6h-CKMB (IU/L)	19.03 ± 7.7	57.41 ± 139.48	0.027	33.34 ± 95.6	92.5 ± 72.3	0.139

GCS: Glasgow Coma Scale; CRP: C-reactive protein; RDW: red cell distribution width; WBC: white blood cells; BNP: brain natriuretic peptide; 6h-TnI: troponin I level 6 h after arrival to ED; ED: emergency department; CKMB: MB isoenzyme of creatine kinase; 6h-CKMB: MB isoenzyme of creatine kinase level 6 h after ED admission; 6h-NT-proBNP: N-terminal pro-B-type natriuretic peptide level 6 h after emergency department admission.

We identified variables predictive for the need of ICU therapy, for complications and a poor outcome, which were included in logistic regression analysis (Table I.4). Patients' age influenced significantly both complications and death (41.2 ± 16.53 years vs. 63.5 ± 7.50 years, p 0.001), age > 60 years being correlated with mortality in intoxication with systemic poisons (OR 0.175; 95% CI: 0.033–0.942, p 0.042). A severe PSS was significantly associated with the need for ICU therapy (71.4% vs. 28.6%, $p < 0.001$), with complications during hospitalization (92.9% vs. 7.1%, $p < 0.001$), and a poor short-term outcome (87% vs. 8.2%, $p < 0.001$). Patients with a moderate PSS were non-significantly distributed among non-complication and complication group (54.2% vs. 45.8%) and had a significant favorable outcome (46.6% vs. 13%, $p < 0.001$). A Glasgow Coma Scale (GCS) < 10 was significantly associated with occurrence of complications (40.7% vs. 4.5%, $p < 0.001$), a poor short-term outcome (65.2%

vs. 10.3%, p < 0.001), and mortality (Tables I.1 and I.3) and predicted death in logistic regression analysis (OR 0.113; CI 95%: 0.019–0.658; p 0.015).

Table I.4. Significant variables for a poor short-term outcome in acute poisoning with systemic toxins, selected using logistic regression analysis.

	Binary		Multinomial	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Initial lactate	2.01 (1.46–2.78)	0.001	1.58 (0.97–2.59)	0.066
4h-lactate	2.56 (1.65–3.99)	0.001		
Initial TnI	9.17 (0.67–124.54)	0.096		
6h-TnI	10.45 (1.15–95.08)	0.037		
Initial CKMB	1.05 (1.02–1.08)	0.002		
6h-CKMB	1.11 (1.05–1.16)	0.001	1.08 (1.01–1.16)	0.018
BNP	1.014 (1.01–1.02)	0.001	1.01 (1–1.02)	0.099
6h-NTproBNP	1.003 (1.00–1.01)	0.006		

OR: odds ratio; CI: confidence interval; 4h-lactate: lactate level within 4 h from admission; TnI: troponin I; 6h-TnI: troponin I level 6 h after arrival to ED; ED: emergency department; CKMB: MB isoenzyme of creatine kinase; 6h-CKMB: MB isoenzyme of creatine kinase level 6 h after ED admission; BNP: brain natriuretic peptide; 6h-NT-proBNP: N-terminal pro-B-type natriuretic peptide level 6 h after ED admission.

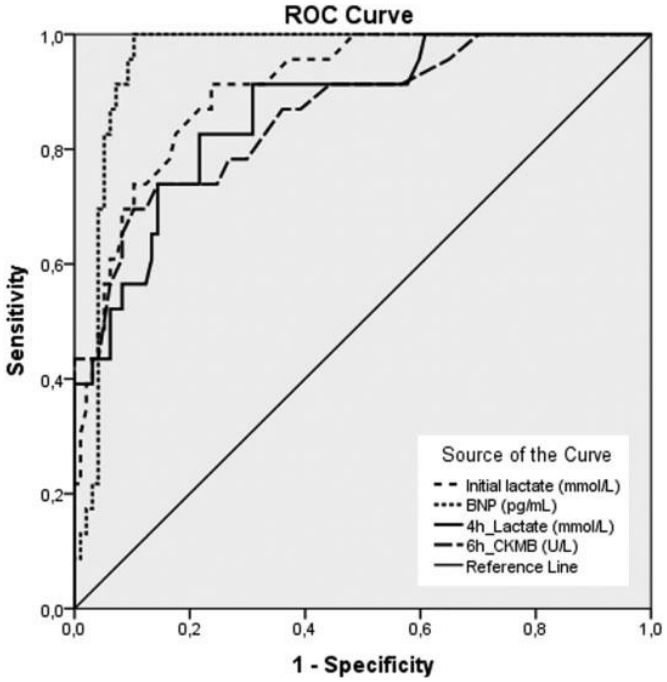
Cardiovascular parameters upon ED arrival, such as heart rate [beats per minute (b/min)] (102.62 ± 32.96 b/min vs. 89.48 ± 21.75 b/min, p 0.025), SBP (110.43 ± 22.83 mmHg vs. 125.72 ± 26.66 mmHg, p 0.016), and diastolic blood pressure (DBP; 67.52 ± 13.45 mmHg vs. 77.09 ± 14.73 mmHg, p 0.007) were correlated with the need for ICU admission. SBP (97.50 ± 39.13 mmHg; p 0.015) and DBP (63.33 ± 29.37 mmHg; p 0.041) were correlated with death but not with occurrence of complications during hospitalization. Among the ECG parameters analyzed using multiple logistic regression analysis, only the QTc interval was predictive for death in our cohort (OR 1.028; CI 95%: 1.01–1.05, p 0.005).

Ethanol co-ingestion had no influence on morbidity, outcome, or death in our cohort. Red cell distribution width (RDW), reported as part of the CBC, was significantly higher in patients with a poor outcome (Table I.1) and in non-survivors (Table I.3), but it was not significantly different within complications groups, in toxic patients who were exposed to systemic poisons (Table I.3). It showed a predictive value for mortality after logistic regression analysis (OR 1.610; CI 95%: 1.01–2.55; p .043). White blood cells (WBC) count was significantly higher in patients who had a poor short-term prognosis, who developed complications, and in non-survivors (Tables I.1, I.3). Also, it was correlated with mortality (OR 1.2; CI 95%: 1.04–1.36; p 0.009) in logistic regression analysis. After acute exposure to a systemic poison, initial arterial lactate level upon arrival at the ED was significantly higher in patients who needed ICU admission (5.29 ± 4.63 mmol/L vs. 2.12 ± 1.65 mmol/L, p < 0.001), who developed complications and in non-survivor group (Table I.3). The 4h-lactate level correlated with complication occurrence, a poor short-term outcome, and death (Tables I.1 and I.3). Using binary logistic regression analysis, we found that both initial lactate (OR 1.46; CI 95%: 1.18–1.80; p 0.001) and 4h-lactate are predictive for mortality (OR 2.75; CI 95%: 1.49–5.04; p 0.001) as well as for a poor short-term outcome (Table I.4) in patients acutely intoxicated with a systemic poison. 4h-lactate correlated with mortality also in multivariate logistic regression analysis (OR 4.87; CI 95%: 0.79–29.82, p 0.087).

Patients in need for ICU therapy had a significantly higher level of BNP on admission (146.53 + 222.64 pg/mL vs. 58.67 + 103.07 pg/mL, p 0.006). Also, BNP was increased in the non-survivor group (Table I.3). The patients with a poor short-term outcome, and who developed complications had on admission a significantly higher BNP, and a higher NT-proBNP level 6 h later (Tables I.1 and I.3). Also, they presented significantly increased values

of initial CKMB and 6h-CKMB (Tables I.1 and I.3), although there was no statistically significant difference of CKMB and 6h-CKMB levels within mortality groups (Table I.3). However, both initial CKMB (OR 1.06; CI 95%: 1–1.12; p 0.033) and 6h-CKMB (OR 1.06; CI 95%: 1.02–1.10; p 0.003) correlated with mortality, in multivariate logistic regression analysis. Logistic regression analysis showed a good correlation of these biomarkers with a poor short-term outcome (Table I.4). Initial TnI and 6h-TnI were significantly increased within poor short-outcome group (Table I.1), but the differences were not statistically significant within complication and mortality groups (Table I.3), and showed no predictive value for mortality, in logistic regression analysis. Several other variables showed significantly statistical differences between means, respectively, frequencies in the groups with and without complications, and within outcome groups (Tables I.1 and I.3). The results of logistic regression applied to variables with significant statistical difference between outcome groups are presented in Table I.4. Validation of predictive variables was performed with ROC methodology (Figure I.2).

We observed all predictive variables, but only four of them had a high value of AUC, demonstrating a very good discriminatory power. The optimal cutoff value for predicting poor short-term outcomes calculated from this ROC curve was: initial lactate > 2.27 mmol/L with a sensitivity of 91.3% and a specificity of 76.3%; BNP > 123.5 pg/mL with a sensitivity of 69.6% and a specificity of 94.8%; 4h-lactate level > 2.63 mmol/L with a sensitivity of 82.6% and a specificity of 70.1%; and 6h-CKMB > 31.50 U/L with a sensitivity of 73.9% and a specificity of 85.6%. Also, we used ROC methodology to observe optimal cutoff value for predicting mortality in these variables: initial lactate level (cutoff point 3.3 mmol/L; AUC, 0.92; CI 95%, 0.86–0.98; p < 0.001), 4h-lactate level (cutoff point 3.7 mmol/L; AUC, 0.98; CI 95%, 0.83–0.88; p < 0.001), BNP (cutoff point 130 pg/mL; AUC, 0.95; CI 95%, 0.91–0.99; p < 0.001), and 6h-CKMB (cutoff point 35.5 U/L; AUC, 0.94; CI 95%, 0.89–0.99; p < 0.001).



Areas under the curves: Initial lactate (lactate obtained upon arrival to ED): 0.91 (95% confidence interval 0.849–0.967, p 0.001); 4h-lactate (lactate level obtained 4h after arrival to ED): 0.87 (95% confidence interval 0.789–0.947, p 0.001); BNP: 0.96 (95% confidence interval 0.921–0.992, p 0.001); 6h-CKMB (CKMB obtained 6 h after ED presentation): 0.86 (95% confidence interval 0.776–0.950, p 0.001). BNP: brain natriuretic peptide; CKMB: MB isoenzyme of creatine kinase; 6h-CKMB: MB isoenzyme of creatine kinase 6 h after ED presentation; ED: emergency department.

Figure I.2. Receiver operating characteristic curves validates discriminatory power of predictive variables for short-term poor outcome.

Discussion

To the best of our knowledge, this study is the first prospective evaluation of the different clinical scores, such as PSS and GCS, in correlation with routine laboratory tests, such as lactate level, cardiac biomarkers and ECG parameters, as predictors for morbidity, short-term outcome, and in-hospital mortality, in patients exposed to various systemic poisons (gases, chemicals, drugs, or plant toxins).

Acute poisonings represent a worldwide problem. In our area, epidemiological data suggested that 97.27% are acute drug poisoning in suicide attempts, using mainly combinations of drugs (32.92%), with a mortality rate of 0.3% (Sorodoc et al., 2011). The majority of drugs ingested in suicide attempts in our study were combination of drugs, sedative-hypnotics, analgesics, and antipsychotics, comparable with the distribution mentioned in reports from the National Poison Data Systems in the United States (Dart et al., 2015). Among non-pharmaceutical agents related with mortality, both in United States and in our area, toxic alcohols, gases (including CO), pesticides, and chemicals represent major concerns (Mowry et al., 2013; Krakowiak et al., 2011). Self-poisoning with organophosphate pesticides is a major health problem in low-income and developing countries, and 200,000 deaths occur annually worldwide (Maignan et al., 2014; Eddleston et al., 2008). Data in our area showed an 11% prevalence of pesticide exposures, with a mortality rate of 3.8% (Gazzi et al., 2014). Some retrospective studies (Akdur et al., 2010; Liu et al., 2013; Kim et al., 2014; Hsu et al., 2013; Kang et al., 2014; Turkdogan et al., 2014; Liu et al., 2014; Pang et al., 2014; Liu et al., 2008) attempted to identify prognostic or mortality indicators in CO poisoning (RDW, lactate, cardiac biomarkers, and copeptine) or in pesticide poisoning (GCS, RDW, serum cholinesterase level, acid–base status, sex, age, and QT interval prolongation on ECG).

Among clinical scores, both PSS and GCS showed a prognostic value in retrospective analysis in some acute poisoning (Akdur et al., 2010; Hu et al., 2010; Viglino et al., 2016). Several studies attempted to quantify the value of GCS in predicting complications, admission to ICU, or mortality, but the results showed different levels of GCS score, with different agents, population, or outcomes studied (Eizadi Mood et al., 2011). Although GCS score is a dynamic variable which varies with time, and interventions applied on toxic patients (i.e., antidote), it was proved to be superior over Acute Physiology and Chronic Health Evaluation (APACHE II), Modified APACHE II Score, and Mainz Emergency Evaluation Scores upon ED admission of patients with mixed drug poisoning induced coma (Eizadi Mood, Sabzghabaee et al., 2011). Our observations showed that a severe PSS and a GCS < 10 at admission in the ED are significantly associated with a poor short-term outcome, the need for ICU admission and early complications in acute intoxication with different types of systemic poisons (drugs, combination of toxins, pesticides, toxic gases, or alcohols). The level of GCS score < 10 is consistent with that assessed prospectively in mixed acute drug poisoning, where it proved to be associated with complication occurrence (Eizadi Mood et al., 2011). In addition, our results showed a predictive role for mortality of this score, in patients acutely exposed to a systemic poison.

An ECG parameter, the QTc interval, proved to have a predictive value for death in acute intoxication with different categories of systemic poisons, not only for pesticides (12.5% patients in cohort studied), antidepressants, or antipsychotics (5.9% cases in our population), as it was showed before in literature (Akdur et al., 2010; Kim et al., 2014; Berling & Isbister 2015; Waring et al., 2010).

A routine test included in CBC, RDW is indicative of anisocytosis in anemias. It has been used to predict outcome in several clinical conditions, such as heart failure, acute coronary syndromes, and peripheral artery disease (De Biase et al., 2013). In clinical toxicology is an independent predictor of 30-day mortality in patients with organophosphate pesticide

poisoning (Kang et al., 2014) and is indicative for the onset of complications in CO acute poisoning (Turkdogan et al., 2014). Our patients had normal hemoglobin levels, and a higher RDW in poor outcome and mortality groups, which we consider to be related with inflammatory processes. It demonstrated in our study a predictive value for death in patients acutely intoxicated with a wide range of systemic poisons, from plant toxins to chemicals and drugs. A high WBC count was reported before in patients poisoned with organophosphate pesticides and CO, who developed complications (Cander et al., 2011; Karabacak et al., 2015). It is probably correlated with the development of oxidative injury, and oxygen-free radicals' activation, as part of a systemic inflammatory process responsible for the development of complications (Waring et al., 2010). We recorded higher values of WBC count in poisoned patients after acute exposure to a systemic poison, in patients with need for ICU therapy, and in the complications group, and this increased the risk of mortality by 20% in our cohort, in patients who developed multiple complications before death.

Hyperlactatemia is an independent predictor of drug-poisoning mortality, with a cut point of 3.0 mmol/L (84% sensitivity, 75% specificity) conferring a 15.8-fold increase in odds of fatality ($p < 0.001$), based on a case-control study, which reported a 5.72% mortality rate (Manini et al., 2010). Other authors found that a selected lactate cutoff point of 3 mmol/L is not an absolute predictor of fatality in drug overdoses, such as beta-blocker acute poisoning (Mégarbane et al., 2010). Furthermore, acidosis caused by elevated lactate levels has been associated with a higher mortality than acidosis due to other underlying causes (Kjelland et al., 2010). Several studies reported that initial arterial lactate value and 12 h lactate metabolic clearance rate are good predictive markers for the outcome of paraquat poisoning (Liu et al., 2013), and that lactate is an useful tool for risk stratification, and predicting hospitalization and fatalities of CO or drug-poisoned patients (Manini et al., 2010; Cervellin et al., 2014). Mixed acidosis influenced the outcome of patients poisoned with pesticides, and acid – base interpretation is well correlated with the severity and death in this poisoning (Liu et al., 2008). After exposure to systemic poisons, we obtained similar correlations between the initial increased lactate level and short-term outcome, complications and death, but we did not find any correlation between lactate metabolic clearance rate and mortality or prognosis. This could be a result of the fact that we used the lactate level 4 h after admission, not 12 h later, as did other authors (Liu et al., 2013). We aimed to identify prognostic indicators early available during the ED stay and, usually, 12 h after hospital arrival, the poisoned patient is already admitted in ICU or a medical ward. Although based on a small number of fatalities (5% in the cohort studied) which may have underpowered the analysis, our results showed that upon ED arrival, the cutoff for initial lactate predicting mortality was 3.3 mmol/L (sensitivity 86%, specificity 88%; p 0.001), consistent with other authors results (Manini et al., 2010), and the cutoff for 4h-lactate predicting mortality was 3.7 mmol/L (sensitivity 83%, specificity 88%; p 0.001).

Specific cardiac biomarkers (such as troponins and natriuretic peptides) were experimentally studied in drug-induced poisoning (Sorodoc et al., 2013). In clinical toxicology, NT-pro-BNP associated with cardiac ultrasound parameters were studied only in CO exposure, where they proved to bring a significant advantage in the diagnosis of patients with myocardial damage (Liu et al., 2014). Myocardial injury assessed in ED upon the arrival of patients severely poisoned with CO independently predicted a short-term poor outcome (Kao et al., 2009). We aimed to estimate the utility as outcome and mortality predictors of cardiac biomarkers in acute exposures to a systemic poison and we excluded possible interferences with acute trauma, burns, and cardiovascular, renal, respiratory, or metabolic chronic diseases by including these pathologies in exclusion criteria. In nondiabetic patients, without history of cardiovascular disease, chronic renal or respiratory failure, acutely intoxicated with systemic

poisons, and assessed 0.5–4.5 h after the exposure, our results demonstrate the benefit of using initial and 6h-CKMB, BNP, and 6h-NT-proBNP as indicators for the need of ICU admission, of early complications, and a poor outcome. Both initial CKMB and 6h-CKMB represented risk factors for mortality in logistic regression analysis. However, the level of TnI showed no correlation with complications, or death.

Some indicators, such as toxicological history, GCS, QT interval, and serum lactate level, proved to be useful to distinguish between low- and high acuity poisoned patients with deliberate drug poisoning, in order to avoid excessive morbidity, after a retrospective analysis (Maignan et al., 2014). Our prospective study provide support for the initial hypothesis that there are some indices available readily, upon the arrival of a patient acutely exposed to a systemic poison (irrespective of type, dose, or route of entrance), such as PSS, a GCS < 10, initial and 4h-arterial lactate level, BNP, and 6h-CKMB, which can early predict complications, poor short-term outcomes, and mortality, whether it is the case of a self-poisoning or an accidental exposure to a toxin. We intend to continue the study including other centers, the population aged < 18 years, and
to continue analysis on categories of toxins, in order to estimate if the toxin itself could be responsible in a larger manner of complications, poor outcome, or mortality rate.

Some limitations in this study should be mentioned. Including patients from a single tertiary center in Romania implies a possible selection bias in the population studied, although the epidemiological and toxicological data are consistent with those reported in other regions (Dart et al., 2015; Maignan et al., 2014). Other prognostic markers, such as APACHE II score, were not reported. We could not calibrate the influence of toxin serum concentration. One other limitation is related to the pitfall of monitoring patients at least 30 days after exposure to systemic poisons.

Conclusions

We concluded that in acute intoxications with systemic poisons, there are several parameters that can be obtained fast, are less invasive, low cost, and are available in every ED, which proved to be helpful in predicting morbidity and mortality: GCS, initial and 4h-lactate level, BNP, and 6 h-CKMB. Thus, the management of these poisonings can be promptly refined in order to address the morbidity and to increase survival rate.

Study on multiple glucose parameters and outcomes in acute poisoning

To our best knowledge, hyperglycemia due to poisoning has been studied only in acute intoxication with methanol and pesticides where it proved to be a prognostic factor for lethality (Sanaei-Zadeh et al., 2011; Moon et al., 2016; Sabzghabaee et al., 2011; Penney, 1988). We have not found any study on non-diabetic and diabetic patients following acute poisoning with undifferentiated xenobiotics to show multiple glycemic parameters with respect to poisoning severity score and outcome. In particular, the predictive value of multiple glycemic parameters for in-hospital mortality is unclear.

Aim of the research

The present study aims to assess if admission blood glucose level (BGL) and glucose variability are associated with the short-term outcomes in both diabetic and nondiabetic acutely poisoned patients admitted within 12 h of exposure to a medical or ICU ward. Thus, the optimal care of critically poisoned patients with hyperglycemia can be improved to decrease the mortality rate among these patients.

Materials and Methods

Study Population

From July 2017 to June 2020, we prospectively enrolled consecutive patients with acute poisoning presented to the Emergency Department (ED) of an urban tertiary hospital with over 100,000 ED visits annually, which is a referral center for clinical toxicology in northeastern Romania. Patients eligible for enrollment were adults older than 18 years, with a diagnosis of acute poisoning within 12 h of exposure to a xenobiotic, as the primary reason for admission, hospitalized in a medical or ICU ward. Patients were excluded if there was a lack of a signed informed consent, were younger than 18 years, had received intravenous dextrose solution, glucocorticoids, catecholamines, glucagon or diazoxide before sampling (Viana et al., 2014; Nikkanen & Shannon, 2007). In addition, patients with another emergency associated (e.g., trauma, burns), or incomplete data were excluded.

Baseline Data Collection

The following data were collected: baseline characteristics, vital signs, mental status, underlying diseases, the Charlson comorbidity index (CCI) calculated according to the well-known scoring system (Charlson et al., 1987), the xenobiotic involved, time from exposure, the intent of the poisoning (self-harm or accident), co-ingestions, laboratory test results upon presentation in the ED and during hospitalization, the poisoning severity score (PSS) grading as (0) none, (1) minor, (2) moderate, (3) severe, and (4) fatal (Persson et al., 1998; Casey et al., 1998), the complications, ICU admission days, and in-hospital outcomes. Based on their CCI score, patients were divided into three groups: mild, with CCI scores of 1–2; moderate, with CCI scores of 3–4; severe, with CCI scores ≥5. The patients were monitored during hospitalization.

Blood glucose samples were obtained on ED admission and subsequently every 3 h for 12 h; after that, upon indication of the attending physician. In cases of hypoglycemia, the glucose level was checked every hour by glucometer until the normal blood glucose levels were obtained. The BGL upon ED admission was measured using the ARCHITECT c16000 clinical chemistry analyzer (Abbott Laboratories, Abbott Park, IL, USA). The BGL upon admission was divided into hypoglycemia (<70 mg/dL), normoglycemia (70–100 mg/dL), impaired glucose level (101–139 mg/dL), and hyperglycemia (>140 mg/dL) ranges, based on the guidelines' threshold for in-hospital hyperglycemia (Moebus et al., 2011; Kavanagh et al., 2010; American Diabetes Association, 2019). We collected all glucose values measured for every patient and calculated the mean glucose level (MGL) during hospitalization and the SD. The mean amplitude of glycemic excursions (MAGE) was defined as the mean of the absolute values of any delta glucose from consecutive measurements that were higher than the SD of the entire set of glucose values (Ali et al., 2008). The mean absolute glucose (MAG) change per patient per hour, defined as the sum of the absolute value of all glucose changes during the time of observation, divided by the total time of observation (mg/dL/h) was calculated (Hermanides et al., 2010). Coefficient of variation (CV) of glucose (SD/MGL, [%]) was derived for each patient.

Outcomes and Definitions

The primary outcome was in-hospital mortality. Secondary endpoints were time spent in the ICU and in-hospital complications related to the poisoning, such as acute liver injury and acute kidney injury, defined according to the guidelines (Chalasani et al., 2014; KDIGO, 2012). We defined the patients discharged without any complication as result of the poisoning as

having a good outcome, a moderate outcome was for the patients with in-hospital complications and a poor outcome was for the patients deceased during hospitalization.

Statistical Analysis

Numerical variables are presented as mean ± SD for normally distributed continuous data, median with interquartile range for non-normally distributed continuous data, or frequency for categorical variables. Independent sample t test or Mann–Whitney U test, as appropriate were used to identify significant differences between the outcome groups defined. The Chi-square test and Cochrane's statistic for categorical variables were used to perform univariate analysis. All variables found to be significant in the univariate analyses for the outcomes were subjected to a multivariate logistic regression analysis. Risk was expressed as odds ratios (ORs) with confidence intervals (CIs). The receiver operating characteristic curve (ROC) was used as a measure of diagnostic performance, to validate the discriminatory power of the model predictive variables. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS (version 22.0; SPSS, Inc., Chicago, IL, USA).

Results

Baseline Characteristics

A total of 1076 patients (51.9% females) were enrolled (Figure I.3).

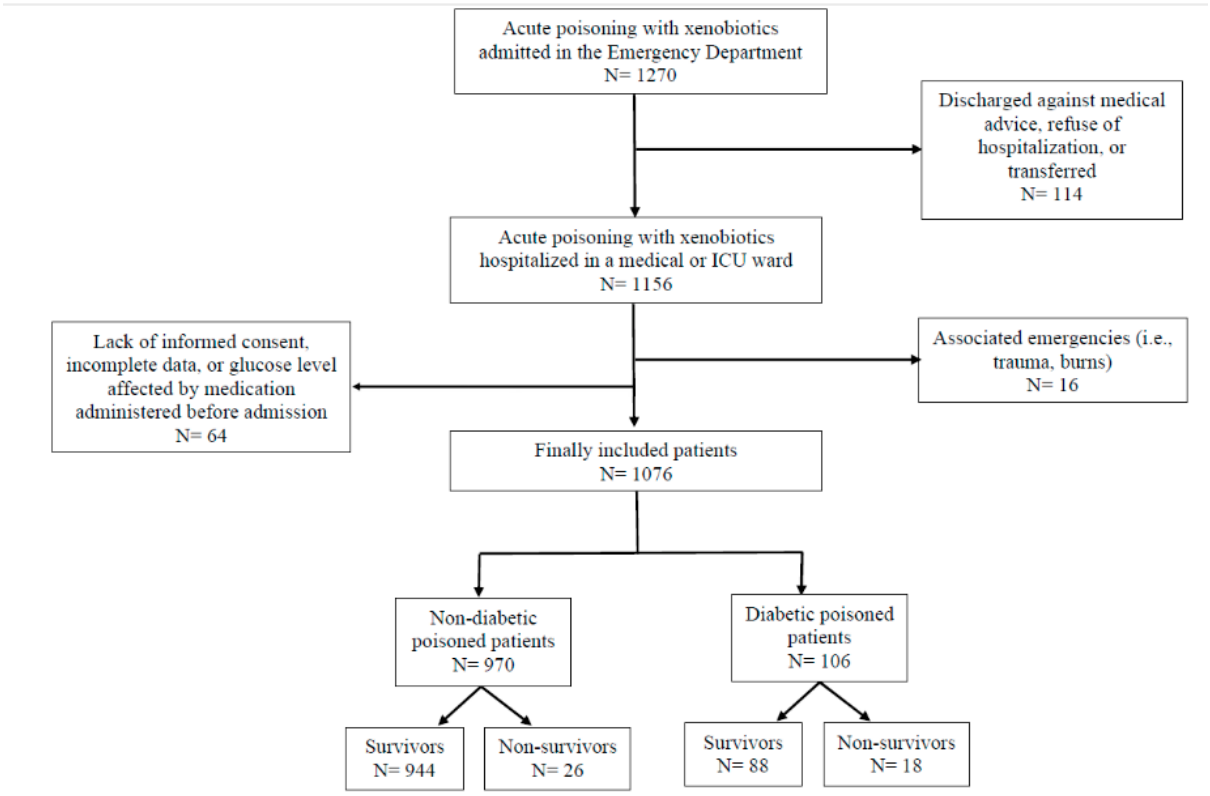


Figure I.3. Study flow diagram.

Median age was 45 years (range 18–98 years), 74.3% had intentional poisoning, 11.6% were overweight, and 11.5% were obese. The median time from poison exposure was 3 h (ranged from 30 min to 12 h). The main categories of poisons involved were prescription drugs

31.5%, pesticides 10.3%, toxic alcohols and chemicals 8.6%, caustic agents 7.7%, toxic gases 5.5%. A combination of poisons was recorded in 26.2% patients. Over-the-counter medication, illicit drugs, or plant toxins represented the rest of the cases (10.1%). Basic characteristics are summarized in Table I.5.

Table I.5. Baselines characteristics of the cohort.

Parameter	Nondiabetic Poisoned Patients (n = 970)	p-Value *	Diabetic Poisoned Patients (n = 106)	p-Value
Age (years)	44 [32–60]	<0.001	57 [42–67.25]	0.083
CCI score (S/N, %)				
CCI 0	96.8/3.2		-	
CCI 1–2	97.9/2.1	0.757	83.1/16.9	0.896
CCI 3–4	98.1/1.9		85.2/14.8	
CCI ≥ 5	97.7/2.3		80/20	
Poison type (S/N, %)				
Combination of poisons	26.8/0.8	0.422	13.2/0	0.021
Drugs/medicines	38.2/0.7		29.2/2.8	
Non-pharmaceuticals	32.2/1.1		40.6/14.2	
GCS (S/N, %)				
≥ 8	81.6/1.5	0.002	58.5/4.7	0.001
< 8	15.7/1.1		24.5/12.3	
PSS (S/N, %)				
Minor	44.3/0		25/0	
Moderate	42.6/30.8	<0.001	53.4/11.1	<0.001
Severe	12.8/65.4		21.6/55.6	
Fatal	0.2/3.8		0/33.3	
SBP (mmHg)	125 [110–140]	0.018	135 [104–153.5]	<0.001
HR (bpm)	84 [73–100]	0.048	91 [75–114]	0.147
pH	7.39 [7.35–7.43]	0.837	7.37 [7.25–7.41]	<0.001
K+ (mmol/L)	4 [3.7–4.3]	0.984	3.9 [3.4–4.43]	<0.001
CRP (mg/dL)	0.37 [0.12–1.49]	<0.001	0.59 [0.15–1.92]	0.189
Hb (g/dL)	13.70 [12.5–14.9]	0.279	13.4 [12.4–14.53]	0.612
BGL (mg/dL)	109 [93–132]	<0.001	221.5 [200.5–266.25]	<0.001
MGL (mg/dL)	109 [94.58–136.25]	0.386	112.84 [94.92–140.19]	0.935
SD (mg/dL)	12.02 [4.51–29.16]	0.759	13.20 [4.95–27.93]	0.658
CV (%)	0.11 [0.04–0.24]	0.781	0.12 [0.05–0.21]	0.915
MAGE (mg/dL)	28 [7–94.25]	0.899	40 [9–117.75]	0.831
MAG (mg/dL/h)	13 [6–28]	0.532	13.55 [5.7–27.31]	0.696
Creatinine (mg/dL)	0.77 [0.69–0.90]	<0.001	0.83 [0.73–1.05]	<0.001
ALAT (U/L)	20 [14–32]	0.133	27 [17–48.5]	0.044
ICU therapy (S/N, %)				
No	82.9/0.2	<0.001	60/1.9	<0.001
Yes	14.4/2.5		22.9/15.2	
ICU hospitalization (days)	4 [3–6]	<0.001	5 [3–7.25]	0.631

Data are presented as median [25–75 percentile], or percentage; *, between survivors (S) and non-survivors (N); CCI, Charlson comorbidity index; GCS, Glasgow Coma Scale score; PSS, poisoning severity score; SBP, systolic blood pressure; HR, heart rate; CRP, C reactive protein; BGL, blood glucose level; MGL, mean glucose level; SD, standard deviation; CV, coefficient of glucose variation; MAGE, mean amplitude of glycemic excursions; MAG, mean absolute glucose change per hour; ALAT, alanine aminotransferase; ICU, intensive care unit.

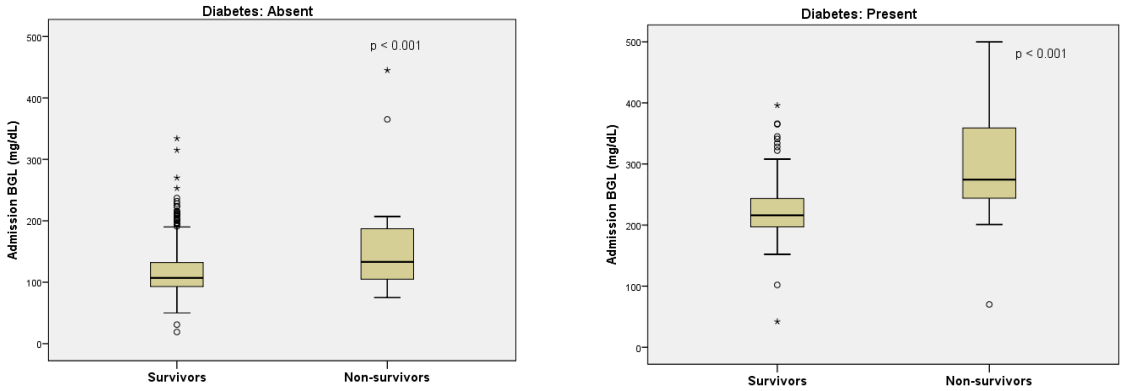
Comorbidities recorded were psychiatric diseases (31.8%), mainly depression (16.9%), and addiction (12.7%), cardiovascular diseases (23.8%), while chronic renal diseases were recorded in 2.6% patients, and chronic liver diseases in 3.7%. Three patients were infected with SARS-CoV2 virus. In total, 214 patients (19.9%) had no associated comorbidities. Complete recovery was observed in 33% of patients, 62.9% developed one or more complications resolved before discharge, and 44 patients died during hospitalization (4.1%). The most frequently observed were CNS (13.2%), gastroenteric and cardiovascular complications (9.8%, and 8%, respectively).

Presence of diabetes was significantly correlated with mortality in acutely poisoned adults ($p < 0.001$). In addition, an altered mental status (GCS < 8), the PSS and the need of ICU therapy were correlated with mortality in both nondiabetic and diabetic patients (Table

I.2.1.5). We found no correlation between gender, poisoning intent, and body mass index (BMI) with mortality in acutely poisoned adults, regardless of diabetes status.

Admission Blood Glucose Level and Outcomes

The admission BGL was not correlated with the BMI of the patients. In addition, it was not correlated with the time after exposure to a xenobiotic. BGL was significantly correlated with mortality both in nondiabetic and diabetic acutely poisoned patients (Table I.5, Figure I.4). The mortality rate in poisoned patients with hyperglycemia upon ED admission was significantly higher as compared with patients with a normal glucose level (65.9% vs. 15.9%, $p < 0.001$). We found that BGL upon admission is significantly correlated with the poison involved (Table I.6) in acutely poisoned nondiabetic patients. Higher BGL was recorded in pesticide poisoning compared with all other groups of poisons analyzed ($p < 0.014$). BGL was significantly higher after exposure to toxic alcohols and chemicals compared with drug poisoning ($p < 0.001$), caustic agent poisoning (p 0.006) and combination of toxin acute poisoning ($p < 0.001$). Acute poisoning with toxic gases resulted in higher BGL upon admission compared with poisoning involving drugs ($p < 0.001$), combination of toxins (p 0.001), and caustic agents (0.044). In addition, significant differences in BGL were recorded in acute poisoning with plant toxins, compared with drug poisoning (p 0.005) and combination of toxins (p 0.018) in nondiabetic adults. However, in diabetic patients, BGL was significantly higher in toxic alcohols and chemicals acute poisoning compared with poisoning with prescription drugs (p 0.02), combinations of toxins (0.001), and pesticides (0.024). Univariate logistic regression revealed that the admission BGL was associated with mortality (OR = 1.015, 95% CI = 1.011–1.019, $p < 0.001$). Multivariate logistic regression (Table I.7) confirmed that admission glucose level was a predictor of mortality (OR = 1.007, 95% CI = 1.002–1.013, p 0.005).



Values are median and interquartile range; dots (°) represent outliers; * represent extreme values (shows non-normal distribution).

Figure I.4. Box plot demonstrating the effect of admission blood glucose levels on mortality.

There was no significant statistical influence of the CCI with regards of mortality in our cohort (Table I.8). ROC curve analysis (Figure I.5) revealed that admission BGL had a good predictive value for in-hospital mortality (area under the curve (AUC) = 0.744, 95% CI = 0.648–0.841, $p < 0.001$). The cut-off value corresponding to the minimal false negative and false-positive results for BGL was 104.5 mg/dL with 84% sensitivity, 41% specificity, 6% positive predictive value, 98% negative predictive value. The admission BGL was significantly correlated with the need of ICU therapy ($p < 0.001$). Time spent in the ICU was significantly increased in patients with a moderate outcome (5.4 ± 4.2 days), and a poor outcome (7.5 ± 6.2

days) as opposed to patients with a good outcome (1.9 ± 0.1 days, p < 0.001). Patients with hyperglycemia (22%) and impaired glucose level (25.7%) upon admission developed significantly more complications during hospitalization, as opposed to patients having a normal glucose level and hypoglycemia upon presentation to the ED (17.9% and 1.4%, respectively, p < 0.001).

Table I.6. Correlation between admission BGL with type of poison involved in nondiabetic and diabetic poisoned adults.

Poison Involved	Nondiabetic Patients (n = 970)	p-Value	Diabetic Patients (n = 106)	p-Value
Prescription drugs	107.67 ± 25.899		233.72 ± 52.949	
Combination of poisons	110.54 ± 27.422		194.79 ± 61.481	
Pesticides	144.05 ± 54.999		227.75 ± 70.404	
Caustic agents	115.26 ± 33.349	<0.001	244.80 ± 80.372	0.066
Toxic alcohols and chemicals	130.86 ± 56.109		280.45 ± 90.574	
Toxic gases	127.77 ± 31.167		257.14 ± 57.389	
OTC	110.65 ± 24.245		231.00 ± 46.669	
Plant toxins	125.45 ± 28.346		203.33 ± 19.009	
Drugs of abuse	120.40 ± 33.721		228.33 ± 98.083	

Data are presented as mean ± standard deviation; OTC, over the counter medicines.

BGL was correlated with the moderate and poor outcomes (Table I.5). The admission BGL was significantly higher in patients with a moderate outcome (130.51 ± 51.1 mg/dL) and a poor outcome (215.05 ± 116.5 mg/dL) as opposed to patients with a good outcome of the poisoning (113.96 ± 36.77 mg/dL, p < 0.001).

Table I.7. Independent predictors of mortality identified with logistic regression analysis including initial glucose level and other statistically significant variables.

Variable	Univariate Logistic Regression			Multivariate Logistic Regression		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Age	1.065	1.033–1.098	<0.001	1.065	1.033–1.098	<0.001
GCS < 8	0.174	0.094–0.321	<0.001	2.774	0.933–8.244	0.066
CRP	1.066	1.023–1.111	0.003	0.992	0.933–1.055	0.804
BGL	1.015	1.011–1.019	<0.001	1.007	1.002–1.013	0.005
ICU therapy	0.019	0.007–0.054	<0.001	0.021	0.005–0.088	<0.001
Creatinine	1.650	1.230–2.212	0.001	1.176	0.813–1.699	0.389
Lactate	1.480	1.35–1.62	<0.001	1.349	1.199–1.517	<0.001

OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale score; CRP, C-reactive protein; BGL, admission blood glucose level; ICU, intensive care unit.

Univariate logistic regression revealed that the admission BGL was associated with in-hospital complications (OR = 1.010, 95% CI = 1.006–1.013, p < 0.001).

Multivariate logistic regression confirmed that the admission BGL was a predictor of a moderate outcome (Table I.9). ROC curve analysis (Figure I.5) revealed that ED admission glucose had acceptable predictive value for in-hospital complications (AUC = 0.618, 95% CI = 0.584–0.653, p < 0.001).

Table I.8. Independent predictors of mortality identified with logistic regression analysis including initial glucose level and CCI.

Variable	Univariate logistic regression			Multivariate logistic regression		
	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age	1.065	1.033-1.098	<0.001	1.063	1.031-1.096	<0.001
GCS < 8	0.174	0.094-0.321	<0.001	3.090	1.001-9.539	0.050
CRP	1.066	1.023-1.111	0.003	0.989	0.929-1.053	0.738
BGL	1.015	1.011-1.019	<0.001	1.008	1.002-1.014	0.006
ICU therapy	0.019	0.007-0.054	<0.001	0.021	0.005-0.088	<0.001
Creatinine	1.650	1.230-2.212	0.001	1.173	0.812-1.695	0.394
CCI 1-2	0.388	0.138-1.090	0.072	0.941	0.189-4.678	0.941
CCI 3-4	0.637	0.223-1.820	0.400	0.826	0.164-4.159	0.817
CCI ≥ 5	0.464	0.142-1.517	0.204	0.407	0.065-2.559	0.338
Lactate	1.480	1.35-1.62	<0.001	1.350	1.198-1.520	<0.001

CCI, Charlson comorbidity index score; OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale score; CRP, C-reactive protein; BGL, admission blood glucose level; ICU, intensive care unit.

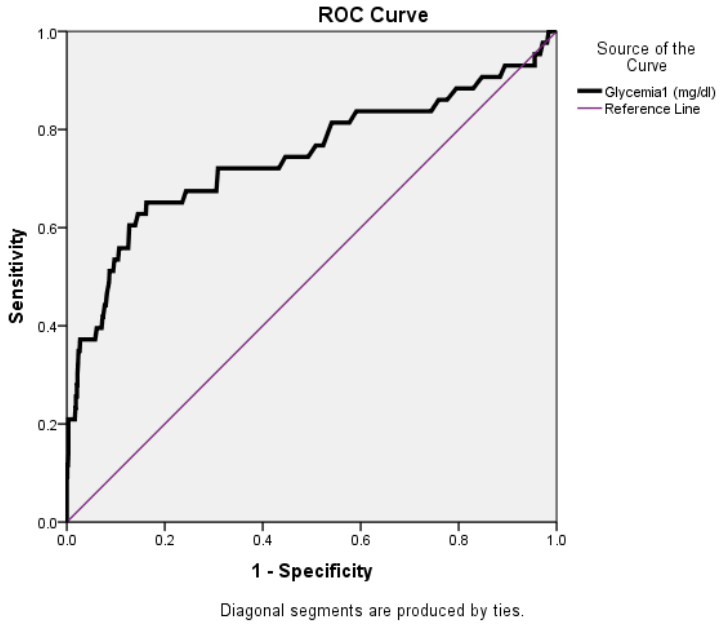


Figure I.5. Receiver operating characteristic (ROC) curve for admission BGL.

Other Glycemic Parameters and Outcomes

When analyzing MGL, SD, CV, MAGE, and MAG with the toxin involved in the poisoning, we observed that in nondiabetic patients, only CV was significantly lower in plant toxin poisoning (0.11 ± 0.12%) as compared with poisoning with OTC medicines (0.18 ± 0.17%, p 0.034), pesticides (0.18 ± 0.15%, p 0.023), toxic gases (0.18 ± 0.18%, p 0.04), and with combination of toxins (0.16 ± 0.15%, p 0.039).

In diabetic poisoned patients, MGL, SD and CV were also correlated with the poison type. MGL was significantly higher in diabetic patients poisoned with OTC medicines (222.25 ± 76.01 mg/dL), as opposed to patients poisoned with prescription drugs (131.62 ± 50.46 mg/dL, p 0.046), caustic agents (128.6 ± 37.95 mg/dL, p 0.05), combination of toxins (126.58 ± 39.96 mg/dL, p 0.042), and pesticides (126.15 ± 85.53 mg/dL, p 0.039).

Table I.9. The significant variables influencing the outcomes.

General Outcome [a]		B	Std. Error	Wald	*p*-Value	OR	95% CI
Moderate	Age	0.009	0.005	3.666	0.056	1.009	1.000–1.018
	Admission BGL	0.005	0.002	5.451	0.020	1.005	1.001–1.009
	Creatinine	0.725	0.354	4.205	0.040	2.065	1.033–4.131
	Lactate	0.086	0.044	3.796	0.051	1.090	0.999–1.188
	GCS > 8	−1.689	0.426	15.695	0.000	0.185	0.080–0.426
	No ICU therapy	−1.259	0.433	8.448	0.004	0.284	0.121–0.664
Poor	Age	0.076	0.017	20.068	0.000	1.079	1.044–1.116
	Admission BGL	0.013	0.004	14.105	0.000	1.013	1.006–1.020
	Creatinine	0.854	0.390	4.802	0.028	2.348	1.094–5.040
	CV	6.758	3.653	3.422	0.064	860.937	0.669–1,107,985.854
	MAG	−0.048	0.026	3.310	0.069	0.954	0.906–1.004
	Lactate	0.385	0.074	26.759	0.000	1.469	1.270–1.700
	No ICU therapy	−5.220	0.866	36.349	0.000	0.005	0.001–0.030

[a.] The reference category is: Good; BGL, blood glucose level; GCS, Glasgow Coma Scale score; ICU, intensive care unit; CV, coefficient of glucose variability; MAG, mean absolute glucose change per hour.

SD was significantly higher in diabetic patients poisoned with toxic alcohols and chemicals (31.07 ± 36.29 mg/dL), compared with poisoning involving combination of toxins (10.64 ± 15.33 mg/dL, p 0.038). CV was higher in diabetic patients diagnosed with toxic alcohols and chemicals acute poisoning (0.19 ± 0.18%, p 0.016) and prescription drugs overdose (0.17 ± 0.12%, p 0.043), versus patients poisoned with combination of toxins (0.07 ± 0.09%). MGL, SD, CV, MAGE, and MAG were not significantly correlated with mortality. However, MAG was significantly higher in patients with a moderate outcome (24.59 ± 28.63 mg/dL/h), compared with patients with a good outcome (20.48 ± 27.3 mg/dL/h, p 0.035), irrespective of diabetes status. After univariate logistic regression, both MGL (OR = 1.007, 95% CI = 1.000–1.013, p 0.034) and CV (OR = 40.578, 95% CI = 1.349–1220.519, p 0.033) were predictive for in-hospital complications (Table I.10).

Table I.10. Variables predictive for in-hospital complications.

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	Admission BGL	.006	.002	10.501	1	.001	1.006	1.002	1.010
	ICU therapy	-1.595	.417	14.619	1	.000	.203	.090	.460
	MGL	.007	.003	4.485	1	.034	1.007	1.000	1.013
	SD	-.025	.013	3.527	1	.060	.976	.951	1.001
	CV	3.703	1.737	4.547	1	.033	40.578	1.349	1220.519
	MAGE	-.003	.002	2.610	1	.106	.997	.994	1.001
	MAG	.012	.007	2.993	1	.084	1.013	.998	1.027
	Age	.010	.004	5.559	1	.018	1.010	1.002	1.018
	GCS < 8	-1.551	.398	15.206	1	.000	.212	.097	.462
	Constant	1.383	.623	4.925	1	.026	3.988		

[a.] Variable(s) entered on step 1: GCS < 8.

CCI was not correlated statistically significant with in-hospital complications in our cohort, although one could expect that an increased number of comorbidities would have an influence on development of complications, in an acute situation, such as acute poisoning (Table I.11).

Table I.11. Variables predictive for in-hospital complications analyzed including CCI score

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Admission BGL	.007	.002	12.090	1	.001	1.007	1.003	1.011
	ICU therapy	-1.630	.414	15.468	1	.000	.196	.087	.442
	MGL	.007	.003	4.362	1	.037	1.007	1.000	1.013
	SD	-.026	.013	3.783	1	.052	.975	.950	1.000
	CV	3.857	1.742	4.900	1	.027	47.303	1.555	1438.542
	MAGE	-.003	.002	2.455	1	.117	.997	.994	1.001
	MAG	.012	.007	2.806	1	.094	1.012	.998	1.027
	CCI 1-2	-.721	.387	3.460	1	.063	.486	.228	1.039
	CCI 3-4	-.534	.398	1.800	1	.180	.586	.269	1.279
	CCI ≥ 5	-.765	.411	3.474	1	.062	.465	.208	1.040
	GCS < 8	-1.535	.396	15.065	1	.000	.215	.099	.468
	Constant	2.442	.714	11.686	1	.001	11.499		

[a.] Variable(s) entered on step 1: Coma.

Discussion

In this cohort of unselected, prospectively followed nondiabetic and diabetic patients with acute poisoning within 12 h of exposure to a xenobiotic, several glycemic parameters during hospitalization were associated with the worst outcomes. While hypoglycemia is a common feature of overdose with sulphonylureas, insulin, ethanol, non-selective betablockers and paracetamol, hyperglycemia is not a common feature of poisonings (Jones, 2016; Lionte et al., 2004). Although acute poisonings represent an important cause of significant morbidity and mortality in patients admitted to the ED, the value of BGL on admission as an outcome predictor had been previously studied only in poisoning with methanol and pesticides (Sanaei-Zadeh et al., 2011; Moon et al., 2016; Sabzghabaee et al., 2011; Mehrpour et al., 2008; Rahimi & Abdollahi, 2007). Several glycemic parameters are associated with mortality and outcomes in different clinical situations, such as pneumonia, exacerbation of COPD, acute coronary syndromes, in cardiac arrest survivors, post-operatively, or in patients admitted in ICU for medical or surgical problems (Garadah et al., 2009; Foltran et al., 2013; Baker et al., 2006; Shohat et al., 2008; Meynaar et al., 2012; Lee et al., 2013; Wang et al., 2020). However, multiple glucose parameters were not studied in nondiabetic and diabetic patients acutely poisoned with xenobiotics.

Our study demonstrated that the admission BGL is important in predicting the outcomes of the hospitalized patients acutely poisoned with xenobiotics, regardless of diabetes status. Admission BGL was a predictor of mortality in acutely poisoned hospitalized patients. We revealed that the in-hospital mortality rate among patients with hyperglycemia upon ED admission was very high. With the exclusion of poisoned patients that received drugs influencing the glucose levels as part of the initial stabilization, we might conclude that hyperglycemia was induced by the stress of poisoning, which is an acute severe illness, inducing significant degrees of metabolic stress, and as a consequence, transient hyperglycemia (Winter et al., 2021). Another explanation could be the toxin's effect on the organs/systems involved in glucose homeostasis (i.e., liver, pancreas). The exact mechanism of the high predictive value of stress hyperglycemia on admission for adverse outcome in acute poisoning

is not known. This could be due to gluconeogenesis, high adrenergic drive, or oxidative stress, similar to the mechanism encountered in other acute clinical situations (Viana et al., 2014; Garadah et al., 2009). In the current study population, the incidence of stress hyperglycemia in accidental and deliberate poisoning with undifferentiated xenobiotics was comparable with previous reports in self-poisoning with agents that do not produce hyper- or hypoglycemia (Sabzghabaee et al., 2011), while the incidence of hypoglycemia was lower in our study.

We found that BGL is correlated significantly with the type of poison, both in nondiabetic and diabetic patients. The incidence of hyperglycemia upon admission is high in patients poisoned with pesticides, toxic alcohols and chemicals, as well as toxic gases. In our cohort, OP pesticides represented the majority of pesticide poisoning recorded. It is known that OPs induce metabolic pathways in brain, skeletal muscles, and liver in favor of increased glucose production, and there is an involvement of oxidative/nitrosative stress. In addition, insulin resistance, disturbed insulin secretion, and pancreatitis are the consequences of OP exposure, which might explain the hyperglycemia recorded in this poisoning (Rahimi & Abdollahi, 2007). The high incidence of hyperglycemia upon admission in both nondiabetic and diabetic patients poisoned with a toxic alcohol that our study revealed can be explained, apart from stress-induced hyperglycemia, by the effect of methanol on the pancreas, acute pancreatitis being a recognized early complication in this toxicity (Sanaei-Zadeh et al., 2011). Hyperglycemia was noticed in acute ethylene glycol (EG) poisoning, both in experimental studies and in clinical settings. EG poisoning can cause transient pancreatitis which results in reduction in serum insulin level; also, an insulin resistance can be seen in association with acute renal failure which develops in EG poisoning within 24–72 h of exposure (Kunnummal Madathodi et al., 2015).

One of the original contributions of the present study is the effect that moderate glucose elevation upon admission has on mortality. In addition, we did not find a significant influence of CCI on short-term hospital mortality and morbidity in this cohort of acutely poisoned patients, similar to other studies involving acutely ill patients (Quach et al., 2009; Yalin et al., 2020). Complications and death were more often present in patients with hyperglycemia (defined as > 126 mg/dL) in a study which assessed deliberate self-poisoning in 345 nondiabetic patients, with a mortality rate of 0.6% (Sabzghabaee et al., 2011). Hyperglycemia is found to be associated with increased risk of infectious complications and septic shock, reduced immune response, dehydration and electrolyte imbalances and lethal multiple organ failure in traumatic and acute ischemic events (Meynaar et al., 2012; Lee et al., 2013; Wang et al., 2020; Bellaver et al., 2019). In our study, hyperglycemia and impaired admission glucose were associated with multiple complications during hospitalization, and we proved that higher glucose levels upon admission had a predictive value for the development of in-hospital complications.

Another original contribution of this study was to show that none of the glycemic parameters with a predictive value for mortality in other categories of medical or surgical patients (Meynaar et al., 2012; Lee et al., 2013; Bellaver et al., 2019) proved efficient in predicting mortality in acutely poisoned patients. Although CV is correlated with the poison type in nondiabetic intoxicated patients, and MGL, SD, and CV are correlated with the toxin involved in poisoned diabetic adults, only MGL and CV proved to be predictive for a moderate outcome in acute poisoning, while MAG is significantly higher in patients with this outcome, irrespective of diabetes presence. MAG was associated with adjusted hospital mortality in surgical patients but not in medical patients (Bellaver et al., 2019). In medical ICU patients, only SD was independently associated with mortality (Meynaar et al., 2012). High glucose variability by itself mediates harm by increasing oxidative stress, endothelial cell damage, mitochondrial damage, and coagulation activation (Lee et al., 2013). Since continuous glucose

sensors are not widely available in many countries, methods using intermittent glucose measurements, such as MAG, have been used instead of measures requiring continuous glucose monitoring (Hill et al., 2011).

Our study has several limitations. First, as a prospective single center study, the results may not be representative of all patients with acute poisoning with a xenobiotic. Thus, a multicenter study should be conducted to confirm our findings. Second, we did not have a standard protocol for monitoring the frequency of blood glucose levels in the first 24 h after admission. The relationship between blood glucose levels and the timing of a last meal before ED admission could not be assessed. However, most patients had at least 3-h delay between exposure to poison and admission to the hospital, with no food being consumed during this period. Third, the number of poisoned patients with DM was too small for conclusions to be drawn on the relation of glycemic variability and outcomes in this subgroup of patients. We did not systematically record HbA1c to be able to analyze the glycemic gap as part of the glycemic variability parameters in this cohort. Finally, there were wide 95% CIs for certain analyses, despite a significant p value, resulting from the relatively small sample size of each group, which implies a lower precision of the sample parameter, so a larger sample size is needed to replicate our results (Sim & Reid, 1999).

Despite these limitations, our study showed that there are significant relationships between glucose variability and short-term outcomes in both nondiabetic and diabetic poisoned adults. In addition, this is the first study to compare different glucose variability parameters in a cohort of patients acutely poisoned with xenobiotics.

Conclusions

This study reveals that several glycemic parameters assessed in acutely poisoned nondiabetic and diabetic patients with xenobiotics, hospitalized in a medical or ICU ward, are predictive for their outcomes. Thus, the admission blood glucose level is predictive for in-hospital mortality and could provide an early risk assessment tool for the patients acutely poisoned with xenobiotics. The mean glucose level and coefficient of variation of glucose after admission are predictive for in-hospital complications' development and might be considered for use as a prognostic tool for short-term outcomes in acutely poisoned patients, hospitalized in a medical or ICU department. High glucose level upon admission in a stressful situation, such as acute poisoning, is correlated with the outcomes. It is useful for practitioners to benefit from this outcome predictor, easily available in the ED, when the patients are admitted within 12 h of exposure to xenobiotics. Whether intervention to prevent either pattern of changing glycemia would affect outcomes in this setting needs further studies.

Study on biomarkers of inflammation and inflammation-related indexes in acute exposure to pharmaceutical and non-pharmaceutical agents

Appropriate risk stratification using biomarkers of inflammation and inflammation-related indexes based on peripheral CBC counts measured in the ED for the need of ICU hospitalization and in-hospital mortality remains a challenge in poisoning with both pharmaceutical and nonpharmaceutical agents. On many occasions, patients are brought in the ED with an altered mental status after being exposed to a xenobiotic, and it is difficult to make a quick prognosis assessment, especially when a toxicological screen or a quantitative measurement of the poison involved is not available or is delayed. High sensitivity CRP, CBC, and inflammation-related indexes based on CBC are readily available in the ED and inexpensive, but no studies have evaluated the prognostic value of these parameters in patients admitted to the hospital with acute poisonings with undifferentiated toxins.

Aim of the research

The primary aim of this study was to investigate whether biomarkers of inflammation and inflammation-related indexes based on peripheral CBC counts measured in the ED are associated with the the need for ICU care, development of complications, and in-hospital mortality and which scores might significantly improve the predictive accuracy for the outcomes in patients acutely poisoned with undifferentiated poisons, including pharmaceutical agents, non-pharmaceutical substances and combination of poisons. We analyzed respiratory, cardiovascular, hepatorenal, gastro-enteral, hematological, metabolic, and CNS complications developed as a direct consequence of intoxication. In order to find out exactly how soon after the poisoning these scores have a prognostic value, we described the changes in the patient's biomarkers of inflammation and inflammation-related indexes in relation with the poison type, within 24 hours of acute exposure.

Materials and methods

Study Design and Setting.

This prospective, observational cohort study was conducted in a university hospital, a tertiary referral center for acute poisonings in North-Eastern Romania. The study was conducted between January 1, 2015, and December 31, 2020. Approval from the local University and Hospital Ethics Committee was obtained for the study, which was conducted in compliance with the guidelines of the Helsinki Declaration. The study complied with the transparent reporting of an observational cohort study (STROBE) and with a multivariable prediction model for individual prognosis (TRIPOD) statement (Collins et al., 2015).

Selection of Participants.

Acutely poisoned adult patients were included in the study and were defined as patients admitted by the ED with accidental or self-poisoning with undifferentiated xenobiotics, including pharmaceutical agents (prescription drugs and over-the-counter (OTC) drugs), street drugs, nonpharmaceutical substances (toxic alcohols and chemicals, OPs, organochlorine pesticides, carbamates, rodenticides, and caustic substances), toxic gases (CO, cyanide, and arsenic), plant toxins (poisonous mushrooms, Aconitum, Datura stramonium, Atropa belladonna, and Nerium oleander), and a combination of poisons within 24 hours of exposure. The exclusion criteria consisted of age (patients younger than 17), pregnancy, known hematologic disease, previous chemotherapy treatment (within the last month), blood transfusion (within the last 2 weeks), a history of autoimmune disease, liver cirrhosis, trauma, burns, temperature more than 37.5°C or ongoing acute infection, discharge against the doctor's orders, and transfer before the final outcome was determined. The following data were collected: age, sex, comorbidities, the body mass index (BMI), the laboratory results upon presentation, the time interval from the poison exposure to the ED arrival, the intentionality of the poisoning, the Glasgow Coma Scale (GCS) score and vital signs upon presentation, CBC counts (neutrophils, monocytes, lymphocytes, and platelets) upon presentation and other biochemistry tests, repeated afterwards upon physician request, and the duration of hospital stay in a medical or ICU department.

Blood Analysis.

Complete blood counts and differentials were studied in the peripheral blood samples: white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, hemoglobin (Hb), platelets, and red cell distribution width (RDW) upon ED admission. Blood samples were taken in calcium-EDTA tubes. CBC were performed with Sysmex XT-4000i-Automated

Hematology Analyzer (Sysmex Corporation, Tokyo, Japan). Inflammation-related indexes based on peripheral CBC counts were calculated as follows: the systemic immune inflammation index (SII) = platelet count × neutrophil count/lymphocyte count; the neutrophil-lymphocyte ratio (NLR) = neutrophil count/lymphocyte count; the monocyte- lymphocyte ratio (MLR) = monocyte count/lymphocyte count; and the platelet- lymphocyte ratio (PLR) = platelet count/lymphocyte count. Arterial blood gases, hs-CRP, and other biochemistry parameters were obtained using ABL 90 (Radiometer, Denmark) and ARCHITECT c16000 clinical chemistry analyzer (Abbott Laboratories, Abbott Park, Illinois, USA).

Data Analysis.

Statistical analysis was performed using SPSS version 22.0 for Windows (IBM SPSS, Chicago, IL, United States) and STATA 13.0 statistical software (Stata-Corp, College Station, Texas, United States). Descriptive variables are expressed as the mean ± SD for data that are normally distributed and as the median and interquartile range (IQR) for variables that are not normally distributed. The $\chi 2$ or Fisher exact test was used to compare categorical values, expressed as percentages. For continuous variables, Student's *t* test or the Mann–Whitney test was used for two group comparisons according to normality. Variables found to be significant in univariate analysis, regarding their correlation with mortality, with a p value of <0.05 were subjected to multivariate logistic regression analysis.

The following variables, which can be easily evaluated upon ED presentation, were tested in the univariate analysis: age, hs-CRP, initial GCS score, arterial lactate, and RDW. In our model, we used RDW-SD (expressed in fL), which is an actual measurement of the width of the red blood cell (RBC) size distribution histogram, because it is not influenced by the average RBC size, as is the situation with RDW-CV (Briggs & Bain, 2012). The first multivariate logistic model included significant univariate predictors (model 1). The significant univariate predictors and NLR were entered into a second multivariate logistic regression model (model 2). Then, NLR in model 2 was successively replaced in subsequent models with the SII (model 3), PLR (model 4), or MLR (model 5). For the multivariate logistic analysis, the NLR, SII, PLR, and MLR were logarithmically transformed using the base logarithm of 2 because of their positively skewed and wide distribution. To avoid multicollinearity, each multivariate model (models 2-5) included one score and other significant univariate predictors. Before modelling, if two or more variables in univariate analysis retained in the multivariate analysis were highly correlated in the linear regression, one variable was removed to avoid collinearity. Estimated odds ratios (ORs) and 95% CIs were calculated for all significant variables. The diagnostic performance of each regression model and each parameter was assessed using receiver operating characteristic (ROC) curves and the corresponding areas under the curve performance. The importance of the effects of clinical and laboratory variables for mortality was graphically represented using the nomogram (Hatmanu et al., 2019). The nomogram is a visualization of a complex model equation, with the aim of representing the behavior of a predictor in scales (Kattan & Marasco, 2010). Kattan-style nomograms were generated in Stata using the nomolog program for binary logistic models (Zlotnik & Abraira, 2015).

Results

We included 1548 patients with a median age of 46 years (range 17-98) who presented to our hospital's ED at a mean of 5 hours (range 30 min to 24 hours) after exposure to a drug, a nonpharmaceutical substance, or a combination of poisons (Figure I.6).

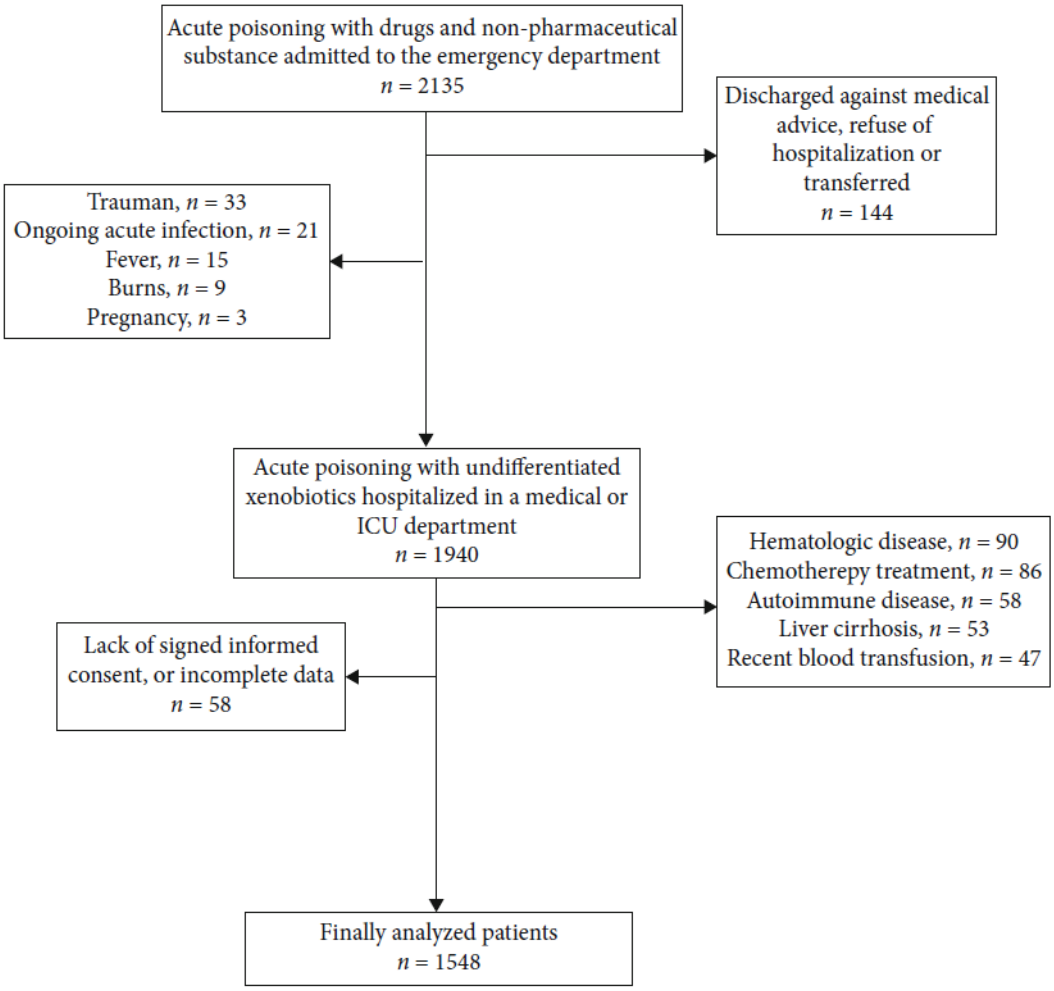


Figure I.6. Study flow diagram.

The baseline characteristics of the cohort are presented in Table I.12. Three hundred and sixteen patients (20.41%) were hospitalized in the ICU, 1072 patients (69.3%) developed complications, and fifty-nine patients (3.8%) died during hospitalization. Associated comorbidities consisted of psychiatric conditions (30.3%), cardiovascular diseases (25.3%), addictions (12.5%), renal diseases (3.6%), respiratory diseases (3.4%), gastrointestinal and hepatobiliary illnesses (4.8%), and diabetes (1.6%). 25.2% of all patients had an abnormal BMI, but this was not correlated with mortality. Based on BMI, no significant differences in leukocytes, platelet count, Hb levels, NLR, MLR, SII, and PLR were recorded.

hs-CRP and CBC Count in Relation with the Outcomes.

When comparing the hs-CRP and CBC count, the non-survivor group had higher hs-CRP, RDW, WBC, lymphocyte, and monocyte counts upon presentation in the ED (Table I.2.1.12). High sensitivity CRP, RDW, WBC, neutrophil, and monocyte counts were significantly associated ($p \leq 0.001$) with ICU hospitalization (Table I.13).

Table I.12. Baseline characteristics of acutely poisoned patients according to mortality.

Variables	Total (n = 1548)	Survivors (n = 1489)	Nonsurvivors (n = 59)	p value
Age (years)	46 [34-62]	46 [33-61]	66 [54-76]	<0.001
Gender (male, %)	729 (47.1)	706 (47.4)	23 (39)	0.127
Intentional exposure (%)	1095 (70.8)	1054 (70.8)	37 (62.7)	0.182
Poison involved (%)				
(i) Prescription drugs	483 (31.2)	468 (31.4)	15 (25.4)	
(ii) Combinations	401 (25.9)	391 (26.3)	10 (13.9)	
(iii) Over-the-counter drugs	67 (4.3)	67 (4.5)	0 (0)	
(iv) Street drugs	35 (2.3)	35 (2.4)	0 (0)	<0.001
(v) Toxic alcohols & chemicals	148 (9.6)	129 (8.7)	19 (32.2)	
(vi) Pesticides	144 (9.3)	138 (9.3)	6 (10.2)	
(vii) Caustic substances (acids, alkali)	125 (8.1)	120 (8.1)	5 (8.5)	
(viii) Toxic gases	86 (5.6)	82 (5.5)	4 (6.8)	
(ix) Plant toxins	59 (3.8)	59 (4.0)	0 (0)	
GCS score < 8 (%)	354 (22.9)	320 (21.5)	34 (57.6)	<0.001
SaO2 (%)	95.89 ± 5.87	96.12 ± 5.11	90.37 ± 14.43	<0.001
HR (b/min)	85 [74-100]	85 [74-100]	90 [75-118]	0.045
SBP (mmHg)	128 [110-142]	128 [111-142]	111 [80-134]	<0.001
Lactate (mmol/L)	1.9 [1.2-3.0]	1.89 [1.2-2.9]	6.6 [1.7-10.4]	<0.001
K+ (mmol/L)	4.0 [3.7-4.38]	4.0 [3.7-4.3]	4.4 [3.7-5.4]	0.001
hs-CRP (mg/dL)	0.37 [0.11-1.49]	0.35 [0.11-1.37]	2.24 [0.26-7.15]	<0.001
WBC (∗1000/mcgL)	9.21 [7.03-12.09]	9.13 [6.91-11.94]	13.21 [9.21-17.47]	<0.001
Lymphocytes (∗1000/mcgL)	2.27 ± 1.41	2.23 ± 1.31	3.08 ± 2.96	<0.001
Monocytes (∗1000/mcgL)	0.36 [0.25-0.52]	0.36 [0.25-0.51]	0.53 [0.33-0.76]	<0.001
Platelets (∗100000/mcgL)	243 [200-286]	244.5 [202-287]	221 [173-268]	0.009
Hb (g/dL)	13.51 ± 1.93	13.52 ± 1.90	13.23 ± 2.65	0.253
RDW-CV (%)	13.2 [12.6-14.1]	13.2 [12.6-14.1]	13.7 [12.9-15.3]	<0.002
RDW-SD (fL)	42.5 [40.2-45.7]	42.4 [40.1-45.3]	48.0 [42.4-51.9]	<0.001
Creatinine (mg/dL)	0.78 [0.70-0.92]	0.77 [0.70-0.90]	1.22 [1.00-1.84]	<0.001
ALAT (U/L)	20 [14-33]	20 [14-33]	31 [16-50]	<0.001
Need for ICU therapy (%)	316 (20.5)	262 (17.7)	54 (91.5)	<0.001
Hospitalization (days)	4 [3-6]	4 [3-6]	7 [2-12]	0.004

Data are presented as median [25–75 percentile], or percentage; GCS: Glasgow Coma Scale; HR: heart rate; SBP: systolic blood pressure; hs-CRP: high sensitivity C-reactive protein; WBC: white blood cells; Hb: hemoglobin; RDW: red cell distribution width; ALAT: alanine aminotransferase; ICU: intensive care unit.

Table I.13. Baseline inflammation biomarkers and related indexes analyzed between the ICU hospitalization group and the non-ICU hospitalization group

Variable	ICU hospitalization group (n=316)	Non-ICU hospitalization group (n=1232)	p-value
hs-CRP (mg/dL)	0.67 [0.10-3.14]	0.32 [0.11-1.15]	<0.001
RDW-SD (fL)	43.4 [40.4-47.4]	42.4 [40.1-45.3]	0.001
WBC (*1000/mcgL)	10.53 [7.69-15.93]	8.93 [6.85-11.51]	<0.001
Neutrophils (*1000/mcgL)	7.19 [4.59-12.20]	6.03 [4.24-8.71]	<0.001
Monocytes (*1000/mcgL)	0.43 [0.28-0.70]	0.34 [0.25-0.49]	<0.001

Data are presented as median [25–75 percentile]

Compared to the patients who had no complications, the patients who developed complications during hospitalization had significantly higher hs-CRP, RDW, WBC, neutrophil, and monocyte counts upon presentation in the ED (Table I.14).

Table I.14. Variables significantly associated with complications' development in poisoned patients

Variable	Complications group (n=1072)	Non-complications group (n=476)	p-value
hs-CRP (mg/dL)	2.28±0.17	1.19±0.18	0.006
RDW-CV (%)	13.57±1.59	13.43±1.64	0.025
WBC (*1000/mcgL)	10.89±5.27	8.84±3.25	<0.001
Neutrophils (*1000/mcgL)	7.98±4.97	6.05±3.08	<0.001
Monocytes (*1000/mcgL)	0.46±0.27	0.35±0.17	<0.001

Data are presented as mean ± SD

The analysis of these parameters based on the group of poisons showed that hs-CRP was significantly higher in patients with caustics poisoning compared with patients intoxicated with combination of poisons, OTC drugs, street drugs, toxic alcohols and chemicals, pesticides, and plant toxins (Table I.15).

Table I.15. Significant differences in hs-CRP levels recorded based on the poison type

Poison	hs-CRP (mg/dL)	p-value
Caustic substances	3.29±5.63	-
Combination of poisons	1.65±4.06	0.003
OTC drugs	0.69±3.7	0.001
Street drugs	0.49±0.56	0.007
Toxic alcohols and chemicals	1.66±3.59	0.01
Pesticides	1.75±4.88	0.019
Plant toxins	1.18±2.69	0.008

Data are presented as mean ± SD

The WBC counts were also significantly higher in pesticides, caustics and toxic alcohols, and chemicals poisoning compared with values recorded in poisoning with a combination of toxins, prescription drugs, and OTC drugs (Table I.16). Regarding RDW, values recorded were significantly higher in poisoning with prescription drugs compared with combination of toxins, pesticides, OTC medications, caustic substances, and plant toxin poisoning (Table I.16).

Table I.16. Changes in RDW and CBC-derived scores based on the poison type.

Poison type	**WBC**	**Poison type**	**WBC**	**p-value**
Pesticides	12.70±6.63	Combinations	9.69±4.43	<0.001
Caustics	11.97±5.02	Prescription drugs	9.09±3.99	
Toxic alcohols and chemicals	11.81±5.92	OTC drugs	8.86±2.79	0.001
Pesticides	12.70±6.63	Plant toxins	10.36±4.32	0.044
Poison type	**NLR**	**Poison type**	**NLR**	**p-value**
Caustics	9.83±18.13	Prescription drugs	3.63±3.16	< 0.001
Plant toxins	8.73±8.73	Combinations	4.20±4.46	
Pesticides	6.95±8.09			
Poison type	**SII**	**Poison type**	**SII**	**p-value**
Caustics	2216.29±3907.97	Prescription drugs	881.56±829.80	<0.001
Plant toxins	2163.72±2627.99			
Pesticides	2006.19±2751.37			
Toxic gases	1696.44±2048.77			0.007
Poison type	**PLR**	**Poison type**	**PLR**	**p-value**
Plant toxins	236.43±239.45	Prescription drugs	134.80±83.63	<0.001
Toxic gases	198.67±225.71			0.003
Caustics	193.86±242.73			0.001
Pesticides	178.07±169.18			0.04

Poison type	MLR	Poison type	MLR	p-value
Caustics	0.55±0.99	Prescription drugs	0.21±0.18	<0.001
Plant toxins	0.50±0.49			<0.001
Pesticides	0.39±0.45			<0.001
Toxic gases	0.38±0.42			0.017
Poison type	**RDW-CV**	**Poison type**	**RDW-CV**	**p-value**
Prescription drugs	13.86±1.95	Combinations	13.32±1.59	<0.001
		Pesticides	13.35±0.99	0.027
		OTC medications	13.28±1.36	0.005
		Caustics	13.20±1.35	0.002
		Plant toxins	13.18±0.83	0.002

Data are presented as mean ± SD

RDW was significantly higher in non-survivors poisoned with pharmaceutical agents and nonpharmaceutical substances (Table I.17, Figure I.7). Interestingly, RDW values were higher in poisoning with toxic gases (13.82 ± 1.48), as opposed to combination of toxins (13.32 ± 1.59, p 0.009), pesticides (13.35 ± 0.99, p 0.031), OTC medications (13.27 ± 1.36, p 0.037), plant toxins (13.18 ± 0.83, p 0.019), and caustic poisoning (13.20 ± 1.35, p 0.006).

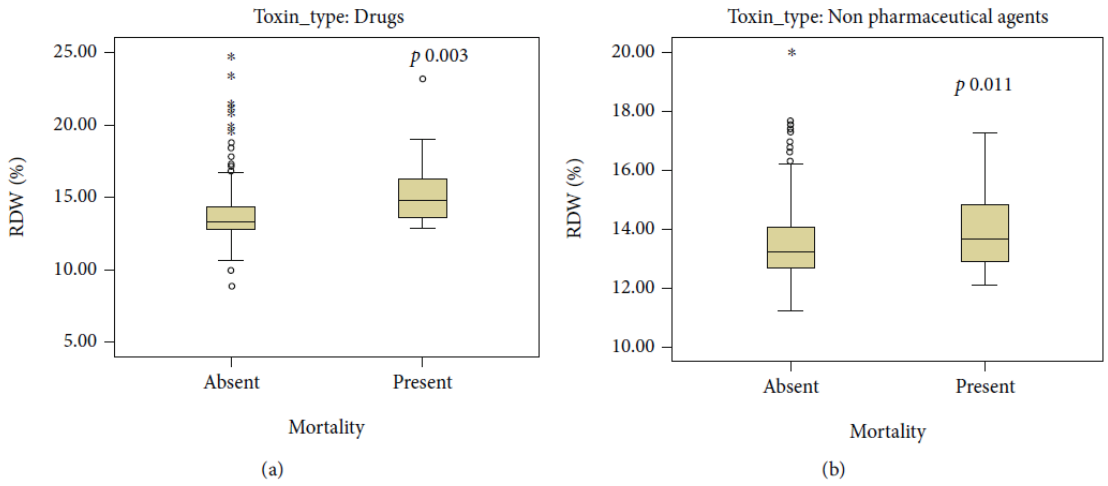
Table I.17. Correlation between admission CBC parameters with the poison type involved.

Poison type	CBC parameter	Survivors (n = 391)	Nonsurvivors (n = 10)	p value
Combination of poisons	WBC	9.62 ± 4.48	13.27 ± 2.72	0.001
	NLR	4.05 ± 4.37	9.67 ± 6.37	0.003
	RDW	13.35 ± 1.55	13.30 ± 2.52	0.444
	SII	1006.15 ± 1201.15	2204.20 ± 2000.29	0.022
	PLR	136.65 ± 86.94	194.83 ± 181.83	0.577
	MLR	0.23 ± 0.24	0.54 ± 0.35	0.003
Pharmaceutical agents	WBC	9.23 ± 3.93	8.94 ± 3.15	0.895
	NLR	3.83 ± 3.71	7.44 ± 4.55	<0.001
	RDW	13.74 ± 1.80	15.36 ± 2.81	0.003
	SII	941.66 ± 943.15	1592.20 ± 975.89	0.001
	PLR	137.60 ± 83.50	243.24 ± 151.82	0.003
	MLR	0.22 ± 0.21	0.42 ± 0.26	<0.001
Nonpharmaceutical substances	WBC	11.56 ± 5.26	16.62 ± 7.80	<0.001
	NLR	7.53 ± 10.95	8.13 ± 15.44	0.194
	RDW	13.44 ± 1.14	14.17 ± 1.64	0.011
	SII	1859.70 ± 2717.59	1828.02 ± 3373.69	0.105
	PLR	187.85 ± 197.95	121.37 ± 186.02	<0.001
	MLR	0.42 ± 0.60	0.45 ± 0.84	0.109

Data are presented as the mean ± standard deviation. CBC: complete blood count; WBC: white blood cells; NLR: neutrophil-lymphocyte ratio; RDW: red cell distribution width; SII: systemic immune inflammation index; PLR: platelet-lymphocyte ratio; MLR: monocyte-lymphocyte ratio.

Inflammation-Related Indexes Based on CBC Count and Outcomes.

The non-survivor group had significantly higher NLR, MLR, and SII values within 24 hours of poison exposure than the survivor group (Table I.18). The analysis based on the main type of the poison involved revealed that NLR, SII, and MLR had significantly higher values in non-survivors poisoned with pharmaceutical agents and combinations, while PLR was significantly higher in non-survivors poisoned with pharmaceutical agents and nonpharmaceutical substances (Table I.17, Figure I.8, Figure I.9, Figure I.10).



(a) patients poisoned with pharmaceutical agents; (b) patients poisoned with nonpharmaceutical substances. Values are median and interquartile range; dots represent outliers; * represent extreme values.

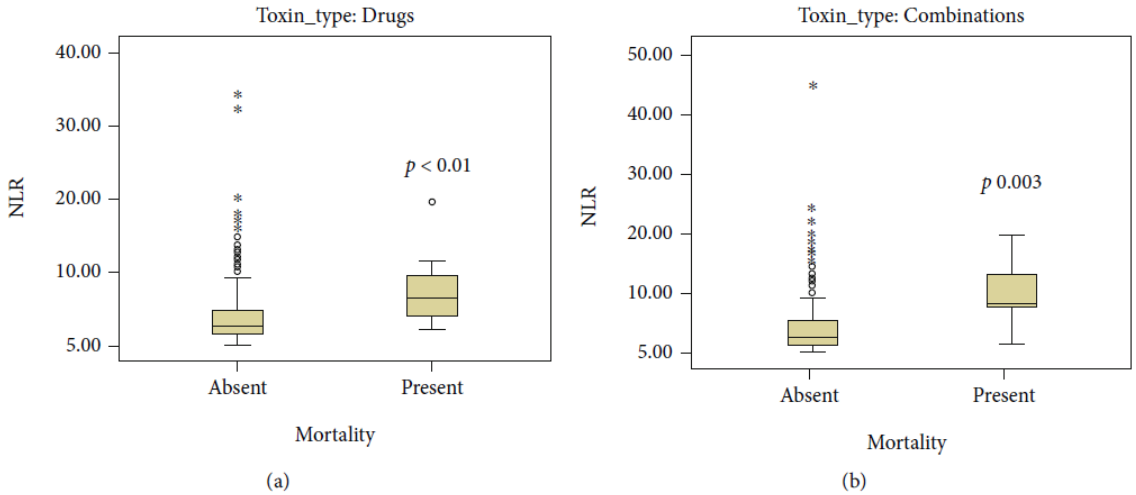
Figure I.7. Box plot demonstrating the effect of admission RDW on mortality.

We attempted to correlate each type of drug with the specific alterations in serum markers in non-survivors vs. survivors (Table I.19). Among non-survivors acutely intoxicated with pharmaceutical agents, cardiovascular drugs were responsible for 15.3%, followed by sedative-hypnotics (5.1%), antiepileptics (3.4%), and antidepressants (1.7%).

Table I.18. Inflammation-related indexes based on CBC count analyzed in respect of mortality and complications.

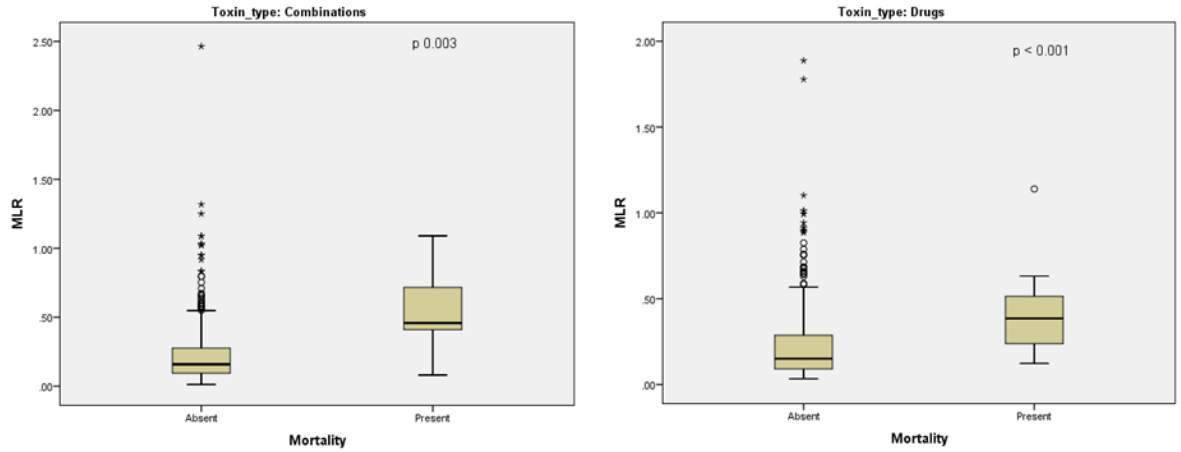
	Survivors	Nonsurvivors	*p* value	No complication	Any complication	*p* value
NLR	2.96 [1.72-5.58]	5.01 [2.26-8.90]	0.007	2.57 [1.56-4.29]	3.20 [1.80-6.62]	<0.001
PLR	119.22 [82.85-178.53]	102.68 [47.74-171.13]	0.598	114.81 [83.16-158.99]	121.21 [81.08-185.12]	0.001
SII	699.70 [393.57-1398.20]	904.98 [416.47-2034.96]	0.030	635.41 [361.25-1035.38]	745.55 [414.41-1693.42]	<0.001
MLR	0.17 [0.10-0.33]	0.28 [0.12-0.49]	0.015	0.15 [0.09-0.26]	0.19 [0.11-0.37]	<0.001

NLR: neutrophil-lymphocyte ratio; SII: systemic immune inflammation index; PLR: platelet-lymphocyte ratio; MLR: monocyte-lymphocyte ratio.



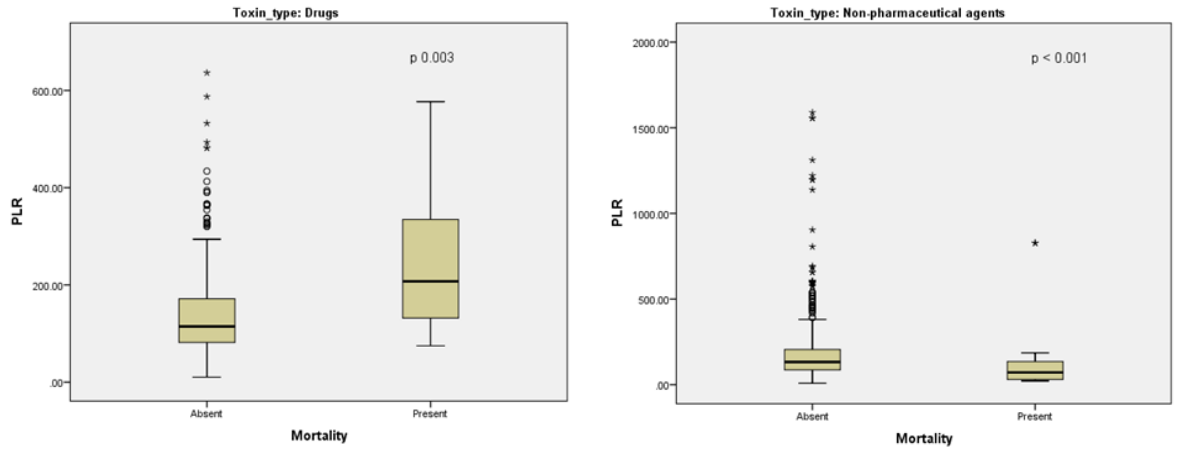
(a) patients poisoned with pharmaceutical agents; (b) patients poisoned with combination of poisons. Values are median and interquartile range; dots represent outliers; * represent extreme values.

Figure I.8. Box plot demonstrating the effect of admission NLR on mortality.



(a) patients poisoned with combination of poisons. (b) patients poisoned with pharmaceutical agents.
Values are median and interquartile range; dots represent outliers; * represent extreme values.

Figure I.9. Box plot demonstrating the effect of admission MLR on mortality.



(a) patients poisoned with pharmaceutical agents. (b) patients poisoned with non-pharmaceutical substances.
Values are median and interquartile range; dots represent outliers; * represent extreme values.

Figure I.10. Box plot demonstrating the effect of admission PLR on mortality.

In our cohort, we identified significant differences between hs-CRP, RDW, NLR, and MLR in cardiovascular drugs poisoning resulting in death, between hs-CRP, NLR, and MLR in poisoning with combinations of drugs/toxins and also between NLR and MLR in deceased patients poisoned with sedative-hypnotics compared with survivors. hs-CRP was significantly higher in non-survivors poisoned with antiepileptic drugs (Table I.19).

No significant correlations were found in antidepressant drugs poisoning, where almost all patients survived (only one deceased patient). NLR had higher values recorded in poisoning with caustics, plant toxins, pesticides, compared with poisoning with prescription drugs, or a combination of toxins (Table I.16).

Also, significant differences were recorded between NLR in toxic gases poisoning (6.68 ± 7.59), compared with poisoning involving prescription drugs (3.63 ± 3.16, p 0.016). SII was significantly higher in poisoning with caustics, plant toxins, pesticides and toxic gases compared with poisoning with prescription drugs (Table I.16).

We noticed significant differences in SII values recorded in poisoning with caustic substances (2216.29 ± 3907.97) as compared with poisoning with toxic alcohols and chemicals (1394.42 ± 1830.62, p 0.011), OTC drugs (1213.89 ± 1240.62, p 0.014), and combination of toxins (1036.18 ± 1237.80, p < 0.001).

PLR was significantly increased in poisoning with plant toxins, toxic gases, caustics, and pesticides compared with prescription drug overdoses (Table I.16). MLR had significantly higher values in poisoning with caustics, plant toxins, pesticides, and toxic gases, compared with prescription drug overdoses (Table I.16).

Also, MLR recorded in poisoning with caustic substances (0.55 ± 0.99) was higher compared with poisoning with OTC drugs (0.27 ± 0.31, p < 0.001), pesticides (0.39 ± 0.45, p 0.04), toxic alcohols and chemicals (0.33 ± 0.44, p < 0.001), and combination of toxins (0.24 ± 0.25, p < 0.001).

Patients with in-hospital complications had significantly higher values of NLR, PLR, SII, and MLR compared with patients with no complications recorded (Table I.18).

We also analyzed CBC parameters predictive for complications in a multivariate analysis, and only RDW and MLR showed a predictive value for this outcome (Table I.20).

Table I.19. Specific alterations in inflammation markers based on the type of drug in non-survivors and survivors' groups.

Variable	Non-survivors	Survivors	p-value
Cardiovascular drugs poisoning			
CRP (mg/dL)	5.42±5.09	2.85±5.25	0.025
RDW (fL)	53.98±10.08	46.02±5.35	0.006
NLR	6.93±5.26	4.06±2.59	0.011
MLR	0.41±0.30	0.24±0.15	0.010
Combination of drugs/toxins poisoning			
CRP (mg/dL)	3.89±2.54	1.61±4.12	< 0.001
RDW (fL)	45.11±6.80	42.65±4.70	0.725
NLR	10.28±6.36	4.23±4.45	0.003
MLR	0.57±0.35	0.24±0.24	0.003
Sedative-hypnotics poisoning			
CRP (mg/dL)	3.53±5.38	1.19±2.27	0.500
RDW (fL)	45.57±0.40	43.12±3.89	0.145
NLR	10.67±1.54	3.01±3.45	0.007
MLR	0.58±0.08	0.17±0.19	0.007
Antiepileptics poisoning			
CRP (mg/dL)	19.12±21.74	2.68±6.35	0.046
RDW (fL)	45.20±6.08	42.39±6.95	0.494
NLR	7.53±1.65	3.63±3.27	0.073
MLR	0.42±0.09	0.21±0.18	0.079

Data are presented as mean ± SD

As for the need of ICU hospitalization, only GCS score < 8, hs-CRP, RDW, and NLR were predictive for this outcome in univariate and multivariate analysis (Table I.2.1.21). The model including hs-CRP, RDW, and NLR upon ED arrival had a significantly higher predictive accuracy for the need of ICU hospitalization (AUC 0.899 [0.876-0.922], p < 0.001, Figure I.11).

Table I.20. Selected factors predictive for complications using univariate and multivariate analysis.

Variable	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age	1.007	1.001-1.013	0.019	1.006	0.999-1013	0.117
Lactate	1.204	1.122-1.292	<0.001	1.129	1.048-1.215	0.001
GCS score < 8	0.800	0.764-0.838	<0.001	0.104	0.063-0.172	<0.001
RDW	3.890	1.456-10.392	0.007	2.889	0.869-9.602	0.083
NLR	1.452	1.277-1.651	<0.001	0.104	0.010-1.028	0.053
SII	1.355	1.203-1.526	<0.001	1.479	0.910-2.405	0.114
PLR	1.144	0.966-1.355	0.119	0.482	0.326-0.712	<0.001
MLR	1.501	1.313-1.715	<0.001	5.201	1.618-16.719	0.006

OR: odds ratio; CI: confidence interval; GCS: Glasgow Coma Scale; RDW: red cell distribution width; NLR: neutrophil-lymphocyte ratio; SII: systemic immune inflammation index; PLR: platelet-lymphocyte ratio; MLR: monocyte-lymphocyte ratio.

Because we aimed to determine which scores have better prognostic value for mortality, the CBC-based scores upon ED presentation were examined by univariate and multivariate analyses (Table I.22). hs-CRP did not correlate with mortality in multivariate analysis, so it was excluded from the final model. To avoid collinearity, the ratios of differential WBC counts (NLR, PLR, SII, and MLR) were entered into different models.

Table I.21. Findings of the univariate and multivariate analysis predictive for ICU hospitalization.

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Age	1.005 (0.999-1.012)	0.116	1.002 (0.989-1.015)	0.769
hs-CRP	1.354 (1.197-1.533)	≤0.001	1.387 (1.162-1.657)	≤0.001
NLR	1.219 (1.087-1.367)	0.001	2.384 (1.709-3.326)	≤0.001
RDW	1.270 (1.127-1.431)	≤0.001	1.382 (1.133-1.685)	0.001
Coma	0.024 (0.017-0.034)	≤0.001	0.016 (0.010-0.024)	≤0.001
Comorbidities present	0.455 (0.309-0.670)	≤0.001	0.602 (0.316-1.147)	0.123
PLR	1.016 (0.900-1.148)	0.794	0.444 (0.300-0.659)	≤0.001

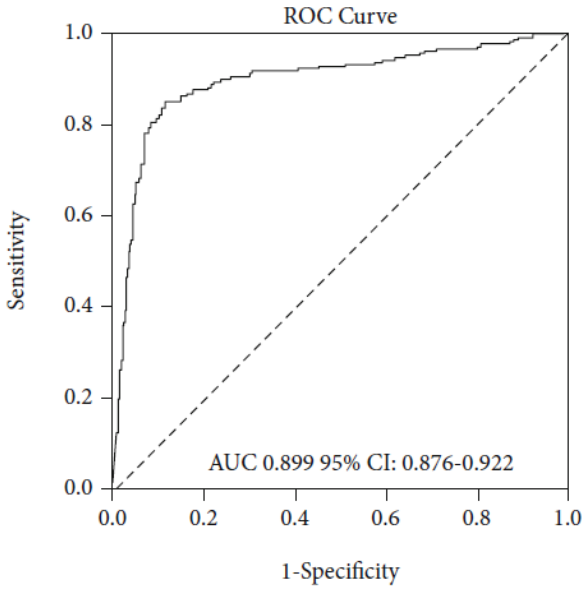


Figure I.11. ROC curve compared the diagnostic accuracy of the model predicting the need for ICU hospitalization.

Age, initial GCS score < 8, arterial lactate, and RDW, which were identified in the univariate analysis as independent predictors for mortality, were tested in the multivariate analysis. In models including each score and the univariate factors, among the scores based on the peripheral CBC count at presentation, only NLR and MLR were significantly associated with mortality (Table I.22).

Table I.22. Univariate and multivariate logistic regression to identify independent predictors for mortality used in the five models.

Age	Lactate	GCS score < 8	RDW	Ln NLR	Ln SII	Ln PLR	Ln MLR
Univariate (OR [95% CI])							
1.05 (1.03-1.06)	1.35 (1.27-1.43)	0.20 (0.126-0.34)	1.14 (1.09-1.18)	1.39 (1.06-1.83)	1.19 (0.91-1.55)	0.64 (0.43-0.96)	1.37 (1.03-1.81)
Multivariate (adjusted OR [95% CI])							
1.06 (1.04-1.09)	1.37 (1.27-1.47)	0.17 (0.09-0.34)	1.08 (1.03-1.14)	—	—	—	—
1.06 (1.04-1.09)	1.37 (1.27-1.48)	0.16 (0.08-0.30)	1.08 (1.03-1.14)	1.47 (1.08-1.99)	—	—	—
1.06 (1.04-1.08)	1.37 (1.27-1.47)	0.17 (0.09-0.32)	1.08 (1.03-1.15)	—	1.23 (0.93-1.63)	—	—
1.06 (1.04-1.09)	1.36 (1.26-1.47)	0.18 (0.09-0.35)	1.08 (1.03-1.14)	—	—	0.96 (0.64-1.46)	—
1.06 (1.04-1.08)	1.37 (1.27-1.48)	0.16 (0.08-0.31)	1.08 (1.02-1.15)	—	—	—	1.43 (1.04-1.96)

GCS: Glasgow Coma Scale; RDW: red cell distribution width; Ln NLR: logarithmically transformed neutrophil-lymphocyte ratio; Ln SII: logarithmically transformed systemic immune inflammation index; Ln PLR: logarithmically transformed platelet-lymphocyte ratio; Ln MLR: logarithmically transformed monocyte-lymphocyte ratio; OR: odds ratio; CI: confidence interval.

The importance of each variable for mortality was graphically shown using the nomogram. Nomograms were built for each model, and the diagrams are presented in Figure I.12 for model 1, Figure I.13 (a) for model 2 and Figure I.13 (b) for model 5. The nomogram which compared NLR, SII, and PLR is presented in Figure I.14. It was constructed using age, arterial lactate upon ED arrival, coma (defined as GCS <8), RDW-SD, NLR, SII and PLR and shows clear the lower significance of SII and PLR compared with NLR.

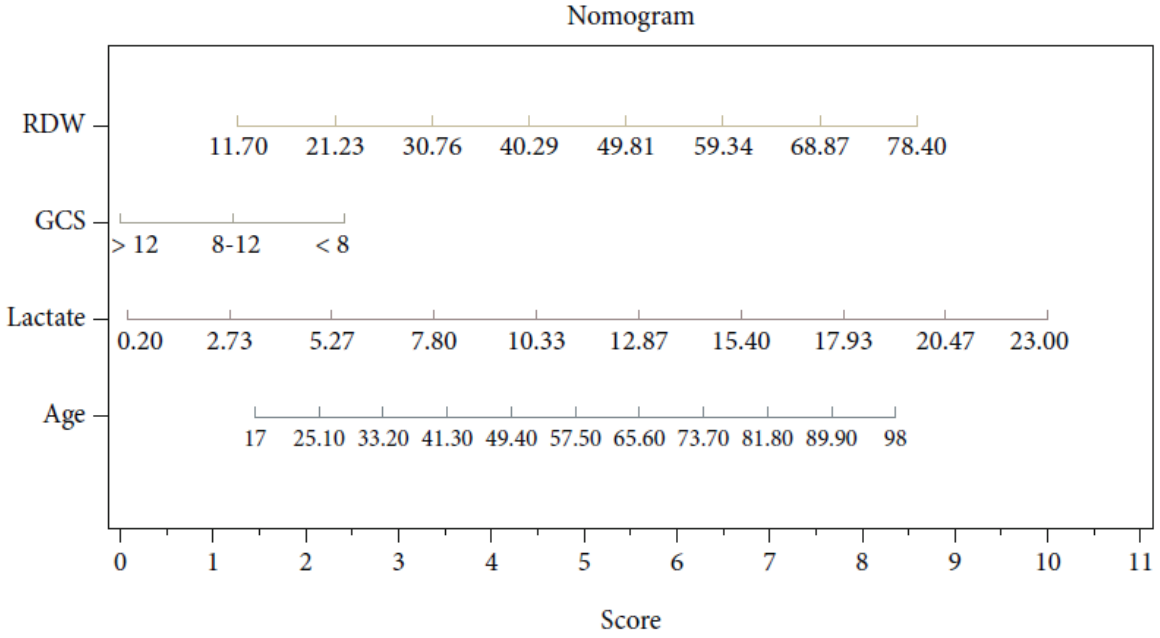
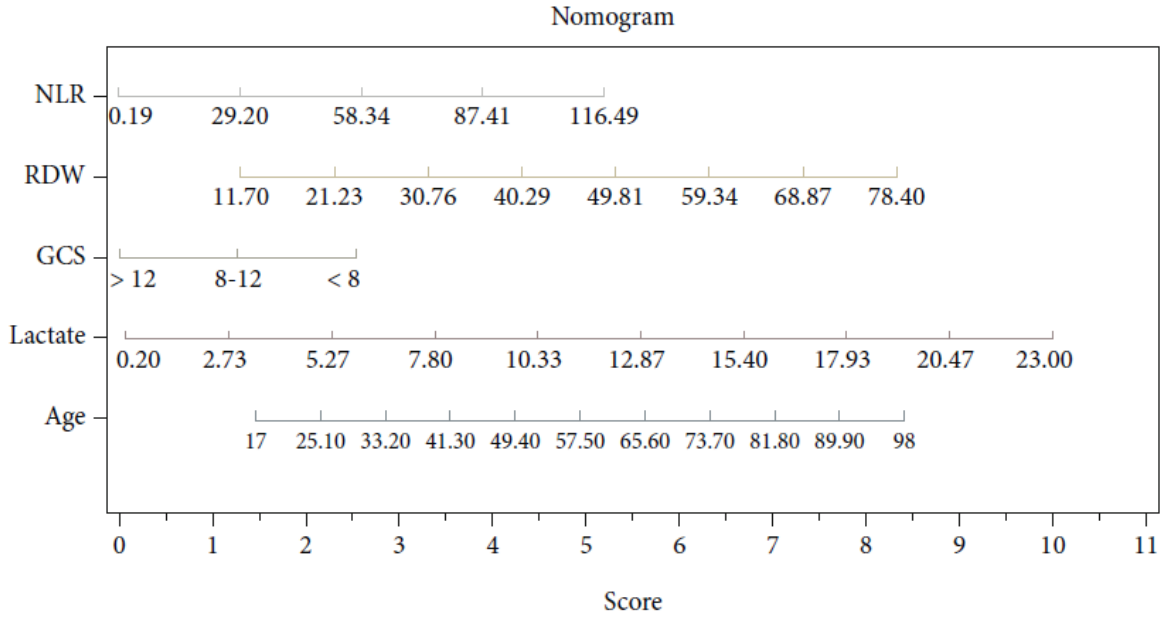
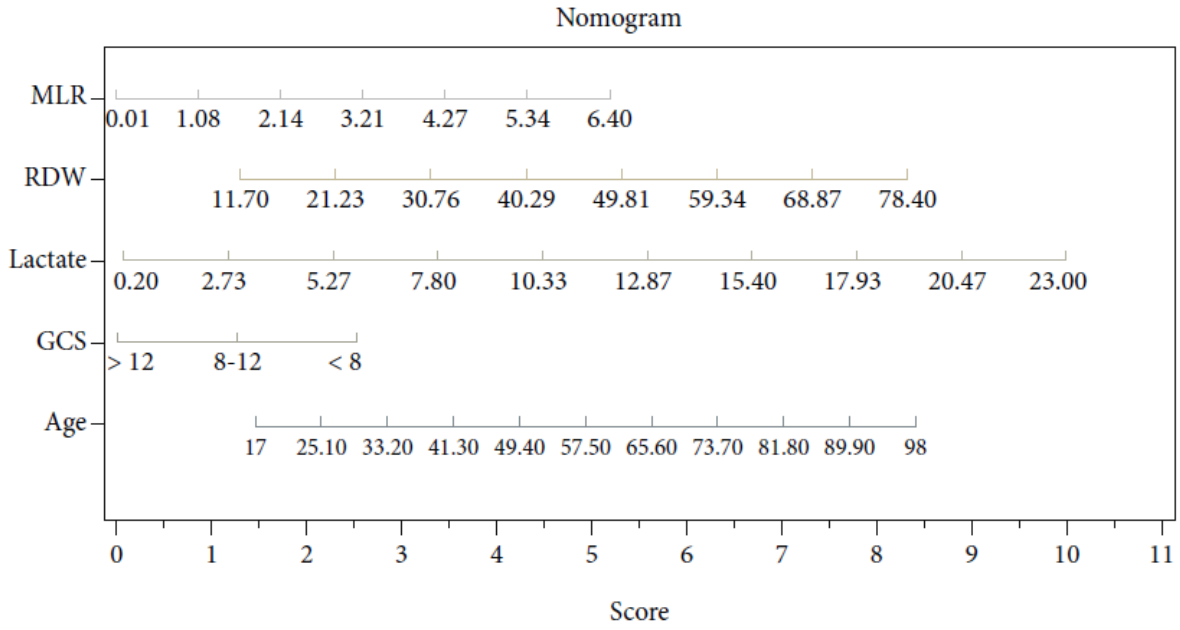


Figure I.12. Nomogram constructed for model 1 included age, arterial lactate upon ED arrival, GCS score, and RDW.



(a) Nomogram constructed for model 2 included all variables in model 1 and NLR.



(b) Nomogram constructed for model 5 included all variables in model 1 and MLR.

Figure I.13. Nomograms built for models 2 and 5.

In the nomogram construction, only the explanatory variables with an important influence on the mortality of the poisoned patients were kept. Comparing the AUCs for each model revealed that the model including the NLR upon ED presentation plus parameters in model 1 (model 2 AUC 0.917 [0.886-0.948]), and the model including the MLR upon ED arrival plus parameters in model 1 (model 5 AUC 0.916 [0.884-0.948]) had a significantly higher predictive accuracy for mortality than the model including RDW alone (model 1 AUC 0.904 [0.864-0.943]; $p < 0.001$, Figure I.15).

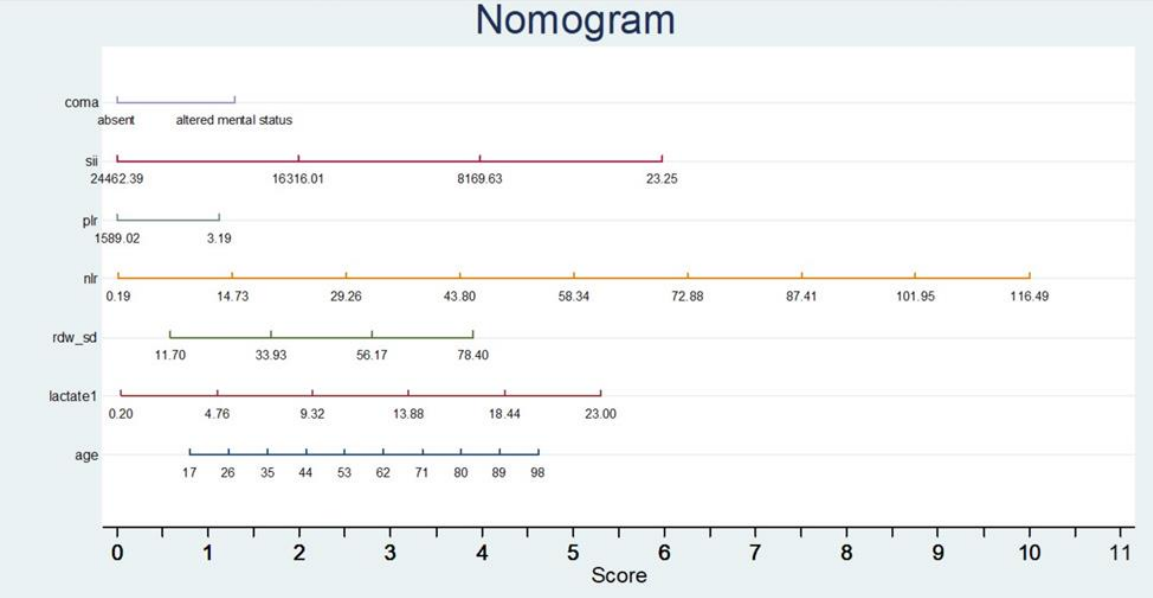
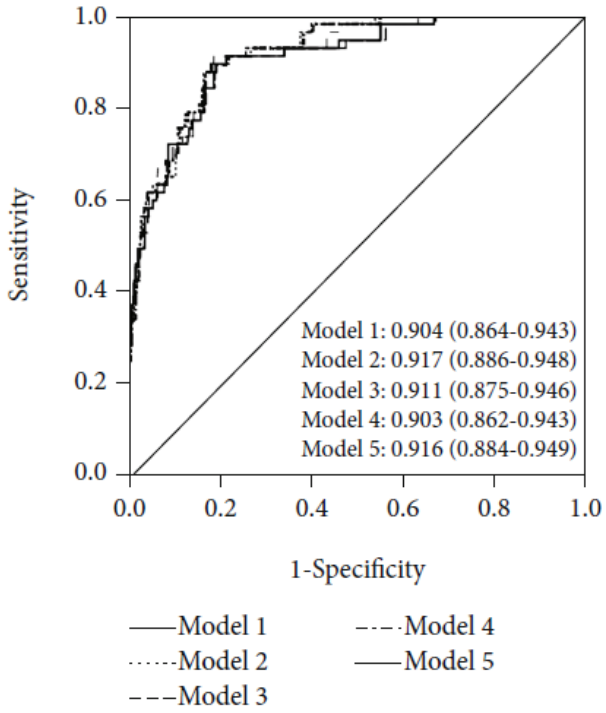


Figure I.14. Nomogram which compares NLR, SII, and PLR.



AUC and 95% CI are presented for each model.

Figure I.15. Receiver operating characteristic (ROC) curves compares the diagnostic accuracy of the five models constructed.

Discussion

Better resource allocation for intoxicated patients in ED will prevent unnecessary admissions to the hospital or ICU, taking into account hospital understaffing and increased number of patients. Also, it will increase the availability of ICU care for those patients that

really need ICU treatment, and it will reduce costs (Brandenburg et al., 2017). To create a better allocation, it is necessary to identify and manage the complicated patients from readily available parameters and accurate prognostic scoring systems, as well as improving benchmarking indices to predict the need for ICU hospitalization, development of complications, and in-hospital mortality when applied to the emergency setting.

This study investigated the predictive performance of inflammation biomarkers and inflammation-related indexes measured in the ED in patients acutely poisoned with undifferentiated xenobiotics. The hs-CRP and complete blood count are routinely determined in all patients presenting with acute poisoning to the ED. These results are usually quick and inexpensive. Several studies revealed the value of hematological parameters in predicting short- or long-term mortality in patients with acute myocardial infarction (Núñez et al., 2008), sepsis and septic shock (Balta et al., 2013), acute pancreatitis (Balta, Demirkol et al., 2013), or in critically ill patients (Akilli et al., 2014). Also, there were studies which analyzed either hs-CRP or hematological parameters in relation with short-term outcomes in poisoning: leukocyte, neutrophil counts, and NLR in paraquat poisoning (Zhou et al., 2016), NLR in mushroom (Koylu et al., 2014) and CO poisoning (Karabacak et al., 2015), hs-CRP (Wu et al., 2016), and RDW in organophosphate poisoning (Dundar et al., 2015). In CO poisoning, it was revealed that there is a correlation between RDW and long-term outcomes (Sunman et al., 2018) and between SII and neurological outcomes (Moon et al., 2019). This is the first study to investigate the relation between the inflammation biomarkers and inflammation-related indexes based on CBC count upon ED arrival with short-term outcomes in patients poisoned with undifferentiated drugs and nonpharmaceutical substances.

The main findings of our study revealed that patients with a need for ICU hospitalization had higher hs-CRP, leukocyte, neutrophil, and monocyte counts, as well as higher dispersion of RBC within 24 hours of exposure to a xenobiotic. In addition, inflammation-related indexes calculated from the peripheral CBC count at presentation were independently associated with short-term outcomes after poisoning with xenobiotics, and among these, only the RDW, NLR, and MLR in combination with clinical and laboratory parameters significantly improved prognostic accuracy for in- hospital mortality and complications. The higher risk patients appeared to be elderly, with increased levels of hs-CRP, RDW, NLR, MLR, and lactate within 24 hours of exposure to a poison. Because these scores are easily measurable upon presentation in the ED, this study could facilitate a quick risk stratification in clinical practice for short-term outcomes among patients with drugs and nonpharmaceutical substances acute poisoning.

Plasma CRP level may be useful for the prediction of prognosis in paraquat poisoning (Ning et al., 2015), and the difference in C-reactive protein value between initial and follow-up after 24 hours was associated with mortality in a study which included 96 subjects with acute organophosphate poisoning (Lee et al., 2013). However, our study showed that hs-CRP has a predictive role only for ICU hospitalization but not for mortality in a larger cohort of patients poisoned with undifferentiated drugs and nonpharmaceutical substances, although there are significant differences in values recorded upon ED presentation based on the group of toxins involved.

Red blood cell distribution width is a measure of the variability in the size of circulating erythrocytes. Although RDW has traditionally been used for the diagnosis of different types of anemia, recent studies reported that RDW is a strong predictor of morbidity and mortality in various clinical conditions, including cardiovascular diseases, community dwelling older adults, or general in-hospital patients (Luo et al., 2016). Acute exposure to various medication increases the risk of adverse drug reactions and toxicity and might lead to high size variation and increased RDW value. We identified higher values of RDW in acute intoxication with

prescription drugs. An elevated RDW is associated with several inflammatory markers, and proinflammatory cytokines could suppress the growth of RBC and decrease the half-life of RBC, which consequently produces an increased RDW (Luo et al., 2016). Another mechanism that can explain the higher levels of RDW in patients who have exposure to different xenobiotics can be related to the acute effect of abnormal hemoglobin molecules on erythrocytes. Carboxyhemoglobin may cause anisocytosis and RDW elevation by making structural changes in erythrocytes (Kaya et al., 2016). Besides the acute effect of CO poisoning, hypoxia is the most important stimulant for increasing erythrocyte production (Sunman et al., 2018). Sulfhemoglobin, which persists for as long as the cell lives, is formed by irreversible oxidation of hemoglobin by drugs (i.e., sulfanilamides, phenacetin, and nitrites) or exposure to sulfur chemicals in industrial or environmental settings (Otto, 2020). Also, many drugs and chemicals can induce methemoglobin formation (i.e., chloroquine, nitroprusside, sulfonamides, organic and inorganic nitrites and nitrates, aromatic amines, and chlorobenzene), as well as some fertilizers and herbicides (Greaves & Hunt, 2010). We also found significantly higher RDW values in acute exposures to toxic gases. Although OPs can induce the formation of free radicals that interact with blood cells by changing hematological parameters (Araoud et al., 2012), the patients with pesticide exposure in our cohort did not have a significantly higher value of RDW, compared with the other groups of poisons analyzed. Oxidative stress is the major mechanism in the pathophysiology of most toxins and diseases (Stohs, 1995). Experimental studies reported that erythrocyte fragility is increased due to the lipid peroxidation of the erythrocyte membrane in cases of severe poisoning, with increased oxidative stress burden, thus increasing the fragility of RBCs and shortening the life-span of RBCs (Luo et al., 2016; Ambali et al., 2010). We tried to avoid other conditions influencing RDW values by excluding the patients whose associated diseases had a well-known relation with RDW, such as liver dysfunction, nutritional deficiencies, bone marrow dysfunction, inflammatory diseases, and chronic or acute systemic inflammation (Dundar et al., 2015).

We consider that in our study, hemoglobin levels of patients poisoned with undifferentiated xenobiotics measured within 24 hours of exposure were not correlated with the outcomes possibly due to nondepleted antioxidant capacity of erythrocytes in the early period of poisoning. Another explanation could be the exclusion of the patients with comorbidities which might affect the Hb and RDW levels from the analysis. However, the RDW cannot provide physicians with accurate information on the inflammatory state and indication of the prognosis of patients with no other inflammatory indicators (Balta et al., 2014), so we thought that it was important to analyze other inflammation-related indexes based on CBC count for this purpose.

The NLR is a combination of 2 independent markers of inflammation: neutrophils, as a marker of ongoing nonspecific inflammation, and lymphocytes, as a marker of the regulatory pathway (Karabacak et al., 2015). In pesticide poisoning, the sensitivity of erythrocytes and lymphocytes to oxidative stress depends on the balance between oxidative stress and antioxidant defense capacity (Hundekari et al., 2013). NLR has been proven to be a useful prognostic factor in many diseases, such as neoplastic disease, stroke, and cardiovascular disease (Moon et al., 2019; Dong et al., 2018). NLR has also been established as a good indicator of systemic inflammatory status in the general population (Imtiaz et al., 2012). Neutrophils are well-known potential biomarkers of inflammation. Since inflammation is responsible for the pathogenic mechanism of tissues injury after poisoning with pesticides, caustic substances, toxic gases or toxic alcohols, and chemicals, the significantly higher neutrophil and NLR values after these acute exposures are not surprising. NLR is more stable than the neutrophil count alone because the neutrophil count is easily affected by infection, stress, or medication, which makes less informative the change in the neutrophil count (Lin et

al., 2017; Moon et al., 2019). It has been extensively indicated that toxicity induced by herbicides is due to a sustained redox-cycling and the subsequent generation of reactive oxygen species, resulting in a general inflammatory reaction (Zhou et al., 2016). An increase in leukocytes and neutrophil counts and a decline in lymphocyte counts are observed when the CBC is evaluated during the acute inflammatory response caused by oxidative stress (Alonso de Vega et al., 2002). The inflammatory and hypoxemic effects of several xenobiotics included in our study might cause a stimulus in the bone marrow and probably induce a release of immature cells or an increase of other cells in the bloodstream, similar with other diseases (Monteiro Júnior et al., 2019). Leukocytosis, neutrophilia, and monocytosis can be detected on CBC in the acute period of the clinical course when the oxidative stress is increased (Dundar et al., 2014).

In our population, NLR and MLR were significantly higher in severely poisoned patients, who did not survive, as well as in patients who developed complications over the course of hospitalization. SII and PLR are commonly used inflammation-related indexes, and we recorded higher values of these parameters in patients poisoned with caustics, pesticides, toxic gases, and vegetal toxins compared with drug overdoses. However, the prognostic accuracy of the models including the SII and PLR in our cohort was not better compared with the models including NLR and MLR. This is in opposition with the results of other studies on SII and PLR, which showed a prognostic accuracy in cancer patients (Zhang et al., 2019; Chen et al., 2021), as well as a good predictive role for neurological long-term complications in CO-poisoned patients (Moon et al, 2019), probably because we were interested only in short-term outcomes and we did not analyze the long-term effect of these indices.

Thrombocytopenia might appear after the oxidative stress which negatively affects the platelet membranes, as it does in all blood cells. Thrombocytopenia is frequently observed in non-poisoning clinical conditions such as sepsis and pneumonia, where the oxidative stress is increased (Dundar et al., 2014). Our results also showed a significant lower platelet count in non-survivors after exposure to different xenobiotics. This might explain the poor value of SII and PLR as predictive variables for mortality and complications in this population. Survivors presented higher platelet counts than non-survivors in our population, which is in line with other reports on patients hospitalized in the ICU (Puertas et al., 2015). Although some poisons, such as CO, induce thrombocytosis and increased platelet activation and the platelets elicit a role in inflammation (Moon et al., 2019), this was not enough to produce a substantial effect when a wide range of poisons, with different mechanisms of action, is analyzed.

Key strengths of our study are the prospective design, the large sample size with a large number of poisons and outcome events, the high proportion of patients with complete data, and the availability of the biomarkers of inflammation and inflammation-related indexes analyzed. The main limitation of our study was that it was single centered. However, our institution is located in northeastern Romania, it is a teaching university hospital and a tertiary referral center for acute poisoning, and therefore it could be used as a representative institution in this region. Another limitation was that the CBC-based parameters were analyzed only at the time of the patients' presentation and were not repeated afterwards in all patients. Additionally, confounding factors interfering with CBC counts might not have been completely excluded, as it is known that diet, exercise, smoking, vitamin supplements, or hormones influence RDW values (Kurtoğlu et al., 2013). Biomarkers of inflammation and inflammation-related indexes only reflect some aspects of the mechanism of acute poisoning with xenobiotics. We might assume that these parameters together with other potential prognostic biomarkers may be more reliable for the evaluation of the short-term outcomes of acute poisoning with pharmaceutical agents and nonpharmaceutical substances upon ED presentation. These findings must be confirmed in prospective, multicenter studies with larger populations.

Conclusions

The present study shows that acute poisoning with undifferentiated drugs, nonpharmaceutical substances, and combination of toxins can cause high levels of biomarkers of inflammation and inflammation-related indexes. High-sensitive CRP, RDW, and NLR have a good prognostic value to predict the need for ICU hospitalization. Only RDW and inflammation-related indexes based on the CBC count, such as NLR and MLR were strongly associated with in-hospital mortality in acutely poisoned patients. Biomarkers of inflammation and inflammation-related indexes derived from the CBC, obtained in an automated way, simple and inexpensive, need to be valued as a daily tool for evaluating prognosis in hospitalized patients with poisoning involving undifferentiated drugs and nonpharmaceutical substances.

Study on cardiac biomarkers in patients with acute dyspnea

The present study was performed to prospectively investigate whether a dual biomarker approach using NT-proBNP and galectin-3 optimizes the diagnosis and risk stratification of acute cardiac dyspnea with a major impact on atypical clinical manifestations and overlapping pathologies.

Patients and methods

Study design and patient population

We prospectively evaluated patients who presented to the ED of a tertiary medical center with sudden-onset or aggravated dyspnea requiring admission in the Department of Internal Medicine. The study was conducted from November 2016 to March 2018. All possible cardiac etiologies of acute dyspnea were accepted as inclusion criteria. Patients were excluded if they required admission to the cardiac intensive care unit or had associated active neoplasia, active liver disease (alanine aminotransferase level of >5 times the upper limit of normal), fibrotic pathologies (e.g., pulmonary fibrosis, collagenosis), or laboratory-based limitations for measurement of galectin-3 according to the manufacturer's instructions (serum cholesterol level of ≥500 mg/dL or serum creatinine level of >5 mg/dL). All procedures for obtaining and documenting written informed consent complied with the Good Clinical Practice and ethical principles for medical research involving human subjects stated in the Declaration of Helsinki. The study was approved by the Ethics Committee of 'Sf. Spiridon' Emergency Hospital, Iasi, Romania and 'Gr. T. Popa' University of Medicine and Pharmacy, Iasi, Romania.

After completion of a standard evaluation (anamnesis, physical examination, laboratory tests, 12-lead ECG, and chest radiography), additional investigations were performed as deemed necessary (abdominal ultrasound, vascular Doppler ultrasound, and computed tomography pulmonary angiography). The NT-proBNP and galectin-3 levels were measured upon admission. The galectin-3 level was determined from serum samples using a chemiluminescent microparticle immunoassay compatible with the ARCHITECT I System (Abbott Laboratories, Chicago, IL, USA). The specificity and sensitivity of NT-proBNP are considered optimal when using age-related cut-offs. Hence, the following cut-off values were used for the study: 450 pg/mL for patients aged <50 years, 900 pg/mL for patients aged 50 to 75 years, and 1800 pg/mL for patients aged >75 years (Wettersten et al., 2016; Maisel et al., 2008). Measurements above these values were defined as elevated values of NT-proBNP. Plasma galectin-3 levels were divided according to data obtained from clinical studies: low risk, <17.8 ng/mL; moderate risk, 17.8 to 25.9 ng/mL; high risk, >25.9 ng/mL (Hrynchyshyna et al., 2013; McCullough et al., 2011; McCullough et al., 2002). The following variables were recorded: age, sex, BMI, smoking habit, alcohol consumption, pathological antecedents, vital

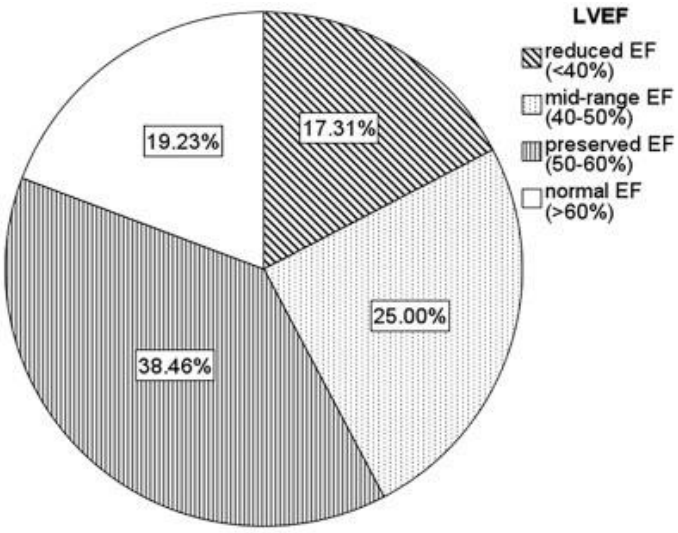
parameters, standard laboratory values, New York Heart Association (NYHA) functional class, glomerular filtration rate (GFR) calculated using the Modification of Diet in Renal Disease Equation, concomitant medication, length of hospital stay, and discharge status. Transthoracic echocardiography (TTE) was routinely performed at patient admission to evaluate the systolic and diastolic function of the left ventricle using a Fukuda Denshi Full Digital Ultrasound System UF-850XTD (Fukuda Denshi Co., Ltd., Tokyo, Japan). Left ventricular systolic function was evaluated based on the following classification of the left ventricular ejection fraction (LVEF): reduced (LVEF of <40%), midrange (LVEF of 40%–50%), preserved (LVEF of 50%–60%), or normal (LVEF of >60%). The patients were divided into two groups according to the etiology of dyspnea: cardiac and non-cardiac. A team of two physicians (A.S. and O.S.) evaluated each patient's medical record.

Statistical analysis

Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test and are presented either as mean ± standard deviation or median with 25^{th} and 75^{th} percentiles. Means between groups were compared using parametric tests (independent-sample t test, analysis of variance followed by the Bonferroni post-hoc test for multiple comparisons) or non-parametric tests (Kruskal–Wallis test, Mann–Whitney U test) as appropriate. In certain cases, logarithmic transformation of data was performed (Jaba & Grama, 2004). Analysis of covariance (ANCOVA) was used to control for the effects that continuous variables such as age or GFR may have on the marker's output between patients with acute cardiac dyspnea and those with non-cardiac dyspnea. For correlations between variables, Pearson's test was used after logarithmic transformation. Measures of associations were studied using phi or Cramer's V (nominal by nominal) and eta (nominal by interval) coefficients. Receiver operating characteristic (ROC) analysis was used to ascertain the diagnostic performance of biomarker levels, and the areas under the curve (AUCs) were compared (DeLong et al., 1988). The diagnostic performance of NT-proBNP and galectin-3 was ascertained for the entire group as well as for certain high-risk subsets such as patients with kidney failure (GFR of <60 mL/minute/1.73m2), age of >60 years, obesity (BMI of >30 kg/m2), rhythm disorders (atrial fibrillation/flutter), LVEF of <40%, arterial hypertension, and type 2 diabetes mellitus. ROC-optimized cut-off values as well as sensitivities and specificities were calculated (Zweig & Campbell, 1993). Data analysis was performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 18.2.1 (MedCalc Software bvba, Ostend, Belgium). All tests were two-tailed, and a p-value of <0.05 was considered statistically significant.

Results

This study included 208 patients ranging in age from 41 to 94 years and with a female to male ratio of 1.44. The patients' NT-proBNP level ranged from 12 to 30,000 pg/mL, and their galectin-3 level ranged from 7.5 to 86.6 ng/mL. The diagnostic criteria for acute cardiac dyspnea were fulfilled in 61.1% of the patients. The cardiac profile of the patients at the time of ED presentation showed that 76.0% were hypertensive and more than half (55.8%) had supraventricular rhythm disorders such as atrial fibrillation or atrial flutter. Chronic myocardial infarction was present in 5.3% of patients. Preserved left ventricular systolic function (50%–60%) defined the largest proportion of patients (38.46%) (Figure I.16).



LVEF, left ventricular ejection fraction.

Figure I.16. Distribution of patients according to the LVEF.

Clinical manifestations compatible with NYHA functional class III to IV heart failure presented a balanced distribution when compared with the subgroup of patients with mild dyspnea (NYHA class I–II) (49.6% vs. 50.4%, respectively). One-third of the patients (30.3%) had associated acute bronchopulmonary manifestations, either community-acquired acute respiratory illness or an exacerbation of a previous chronic bronchopulmonary condition (chronic obstructive pulmonary disease or bronchial asthma). Anemia, chest wall syndromes (costochondritis, musculoskeletal pain), diseases of the digestive system (gastroesophageal reflux), and anxiety were encountered among other non-cardiac etiologies of acute dyspnea. Other comorbidities were obesity (BMI of >30 kg/m2; 30.3%), type 2 diabetes mellitus (28.4%), chronic stroke (18.6%), chronic kidney disease (15.4%), lower extremity peripheral arterial disease grade II to IV (14.4%), and chronic bronchopulmonary pathology (10.1%).

Commonly associated medications at admission included beta-blockers (49.5%), diuretics (42.3%), antiplatelet drugs (32.7%), and angiotensin-converting enzyme inhibitors (27.4%). Alcohol consumption was classified as "yes," "no," and "former." Chronic alcohol consumption was present in 12.5% of the study group (n=26) and was linked to an altered LVEF (consumer, 44.19% ± 10.64%; non-consumer, 51.39% ± 9.47%; former consumer, 49.69% ± 7.38%; p 0.005), an increased alanine aminotransferase level as an indicator of impaired hepatic function (consumer, 37.96 ± 27.64 U/L; non-consumer, 25.49 ± 16.39 U/L; p 0.012), and a proinflammatory status as reflected by the serum C-reactive protein level (consumer, 6.83 ± 11.81 mg/dL; non-consumer, 2.47 ± 4.75 mg/dL; p 0.027). Additionally, higher estimated GFRs were noted in the subgroup of chronic alcohol consumers (consumer, 77.23 ± 28.8mL/minute/1.73m2; non-consumer, 71.73 ± 25.01mL/minute/1.73m2; p 0.042). Smoking habits were found in 20.2% (n=42) of the patients but did not lead to any significant differences in the biomarker levels or LVEF between the cardiac and non-cardiac dyspnea groups.

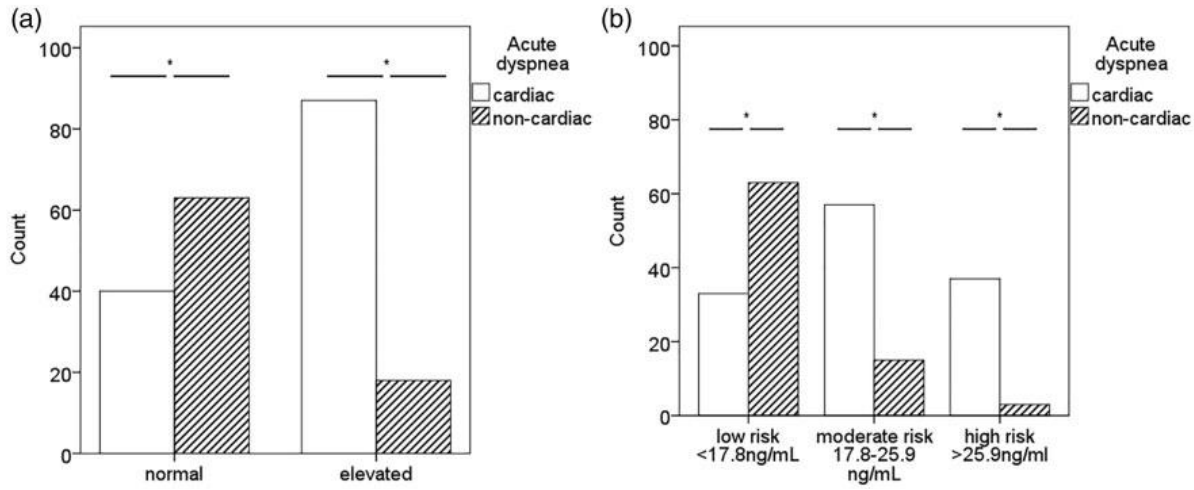
Patients with acute cardiac dyspnea were significantly older ($p < 0.001$) and had a significantly longer in-hospital stay (p 0.032). The heart rate was higher ($p< 0.001$) and the LVEF was lower ($p< 0.001$) in the cardiac than non-cardiac dyspnea group. Biochemical characteristics of the patients with acute cardiac dyspnea included increased serum levels of urea and uric acid ($p< 0.001$ for both) and significantly lower GFRs (p 0.009) compared with the patients with non-cardiac dyspnea ($p<0.05$) (Table I.23).

Table I.23. Comparison between cardiac and non-cardiac dyspnea groups.

	All patients	Acute cardiac dyspnea	Acute non-cardiac dyspnea	p-value
Age, years	72.96 ± 11.11	75.96 ± 10.18	69.14 ± 11.49	0.000*
Hospitalization, days	7.27 ± 3.45	7.61 ± 3.42	6.74 ± 3.46	0.032*
HR, beats/minute	91.99 ± 25.78	98.06 ± 27.68	82.46 ± 19.06	0.000*
GFR, mL/minute/1.73 m^2	72.69 ± 25.68	67.50 ± 26.93	80.82 ± 21.33	0.009*
Serum level of urea, mg/dL	50.47 ± 26.94	56.70 ± 30.71	40.71 ± 15.28	0.000*
Serum level of uric acid, mg/dL	5.89 ± 2.66	6.26 ± 2.92	5.30 ± 2.07	0.000*
LVEF, %	50.38 ± 9.76	46.60 ± 9.43	56.32 ± 6.95	0.000*

Data are presented as mean ± standard deviation. HR, heart rate; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction.
*p<0.05.

Both biomarkers followed in this study, NT-proBNP and galectin-3, were significantly higher in the patients with acute cardiac dyspnea than in those with acute noncardiac dyspnea (p<0.001) (Figure I.17).



*p<0.05. NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

Figure I.17. NT-proBNP (a) and galectin-3 (b) levels based upon acute dyspnea groups.

Several parameters showed a significant association with the etiology of acute dyspnea: age, elevated systolic blood pressure, LVEF, presence of atrial fibrillation/flutter, and GFR. Additionally, both biomarkers (Table I.24) had a strong and significant connection with the etiology of dyspnea (p<0.001 for both).

The serum concentrations of both NT-proBNP and galectin-3 were significantly higher in patients with acute cardiac dyspnea (Table I.25) than in those with non-cardiac dyspnea (p<0.001 for both). ANCOVA was performed to determine whether the differences observed in the NT-proBNP and galectin-3 levels between patients with cardiac and non-cardiac dyspnea were indeed due to the type of dyspnea and not solely to the influences that factors such as older age or impaired GFR may exert on these markers. After controlling for the differences between patients with cardiac and non-cardiac dyspnea with respect to age (higher in patients with cardiac dyspnea) and GFR (impaired in patients with cardiac dyspnea), ANCOVA was performed to assess whether patients with cardiac dyspnea still had higher levels of NT-proBNP than patients with non-cardiac dyspnea.

Table I.24. Profile of acute cardiac and non-cardiac dyspnea groups.

Parameter	All patients (n)	Dyspnea etiology groups		Measures of association with dyspnea etiology groups	
		Cardiac (n)	Non-cardiac (n)	Coefficient	p-value
Total number of patients	208	127	81		
Age of >60 years	181	115	66	0.193	0.021*
Male sex	85	55	30	0.062	0.370
Smoking	20	11	9	0.61	0.677
Elevated NT-proBNP, pg/mL	105	87	18	0.451	0.000*
Elevated galectin-3, >17.8 ng/mL	112	94	18	0.516	0.000*
GFR of <60 mL/minute/1.73 m^2	66	52	14	0.267	0.005*
SBP of >140 mmHg	115	60	55	0.228	0.029*
LVEF of <40%	36	33	3	0.512	0.000*
Rhythm disorders (atrial fibrillation/flutter)	116	97	19	0.520	0.000*
Type 2 diabetes mellitus	59	37	22	0.021	0.758
Obesity (BMI of >30 kg/m^2)	63	39	24	0.095	0.598

NT-proBNP, N-terminal prohormone of brain natriuretic peptide; GFR, glomerular filtration rate; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; BMI, body mass index.

Table I.25. NT-proBNP and galectin-3 in subgroups of patients with associated risks.

Subgroups	NT-proBNP (pg/mL)			Galectin-3 (ng/mL)		
	Cardiac	Non-cardiac	p-value	Cardiac	Non-cardiac	p-value
All patients	3137 (829–7933)	543 (166–1065.5)	0.00**	22.3 (17.5–28.4)	15.7 (12.6–17.8)	0.00**
Age of >60 years	3508 (829–9261)	613.5 (212.8–1203.5)	0.00**	22.4 (18.6–29.2)	15.7 (12.3–17.8)	0.00**
Obesity (BMI of >30 kg/m^2)	2325 (736–4570)	344 (89.7–744.8)	0.00**	22.8 (19.2–29.2)	16.05 (14.5–17.9)	0.00**
GFR of <60 mL/minute/1.73 m^2	4246.5 (1301–10592.3)	1254.5 (530–4783)	0.00**	24.65 (19.9–34.6)	15.95 (13.3–19.3)	0.00**
LVEF of <40%	5810 (3230–10131)	173 (139.5–1119)	0.011*	22.8 (19.6–28.5)	17.9 (14.8–18.7)	0.045*
Rhythm disorders (atrial fibrillation/flutter)	3508 (893.5–7829)	1081 (390–2706)	0.00**	22 (17.1–26.2)	14.8 (11.7–15.9)	0.00**
Type 2 diabetes mellitus	2567 (882–8033.5)	326.5 (104.3–816.8)	0.00**	22 (18.6–31.8)	16.65 (14.6–18.1)	0.00**
Arterial hypertension (SBP of >140 mmHg)	2909.5 (696.25–9291.25)	556 (194–1167)	0.00**	22 (17.4–30.9)	15.8 (13.4–17.6)	0.00**

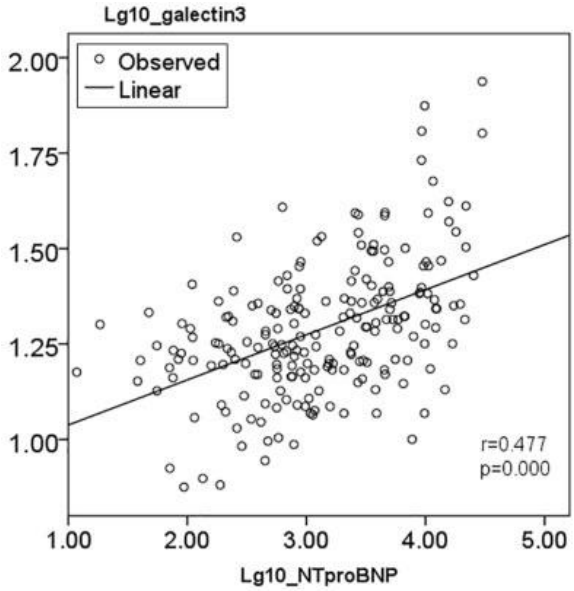
Data are presented as median and interquartile range (25th–75th percentile). NT-proBNP, N-terminal prohormone of brain natriuretic peptide; BMI, body mass index; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure. *p<0.05, **p<0.001.

The same analysis was performed for the second marker evaluated in this study (galectin-3). The results indicated that after controlling for the differences in age and GFR between patients with cardiac and non-cardiac dyspnea, the differences in NT-proBNP

[F=16.81(1,204), p<0.001] and galectin-3 [F=22.45(1,204), p<0.001] between the two groups remained significant. The adjusted group means and variability (standard error) after controlling for differences in age and GFR as covariates were as follows: cardiac acute dyspnea: NT-proBNP, 5002.977±450.4 pg/mL and galectin-3, 23.785±0.823 ng/mL; non-cardiac acute dyspnea: NT-proBNP, 2020.745±551.913 pg/mL and galectin-3, 17.485±1.009 ng/mL. These findings indicate that the type of dyspnea significantly influences the levels of NT-proBNP and galectin-3.

Among all patients enrolled in this study, 4.3% (n=9) died before discharge from the hospital and 2.9% required transfer to the coronarography unit for acute coronary syndrome and revascularization procedures. In the subgroup of patients who died of cardiac causes (n=8), the serum galectin-3 levels were significantly higher and ranged from 17.8 to 63.4 ng/mL [cardiac median, 29.2 ng/mL; interquartile range (IQR), 24.7–36.5 ng/mL and non-cardiac median, 20.1 ng/mL; IQR, 11.7–28.5 ng/mL; p 0.038]. For NT-proBNP, these values ranged from 897 to and 30000 pg/mL (p 0.003).

The patients were divided into three subgroups according to their outcome at discharge: deceased, aggravated, and improved. Both NT-proBNP and galectin-3 showed significant differences among these subgroups. The differences were very significant between the deceased subgroup [median galectin-3, 28.5 ng/mL (IQR, 21.05–36.55 ng/mL); median NT-proBNP, 9599 pg/mL (IQR, 4284–16235 pg/mL)] and improved subgroup [median galectin-3, 18.6 ng/mL (IQR, 15.2–23 ng/mL); median NT-proBNP, 1132 pg/mL (IQR, 432.5–4184.5 pg/mL)] (NT-proBNP, p 0.001; galectin-3, p 0.012). Statistically significant differences between the deceased and survivors (improved or aggravated) subgroups were observed for age (improved, 72.5±11.20 years; deceased, 79.78±10.09 years; p 0.043), the serum C-reactive protein level (improved, 2.39±5.3mg/dL; deceased, 11.72±10.01mg/dL; p<0.001), and hyponatremia (serum sodium level of <135mmol/L) (improved, 138.65±4.89mmol/L; deceased, 134.44±5.22mmol/L; p 0.031). Inclusion in a certain NYHA functional class weightily influenced the outcome at discharge as shown by significant differences in the categorization in different NYHA classes between the deceased and survivor groups (p 0.02). The correlation between the NT-proBNP and galectin-3 levels was direct (Figure I.18), moderate to strong (r=0.477), and significant (p< 0.001).

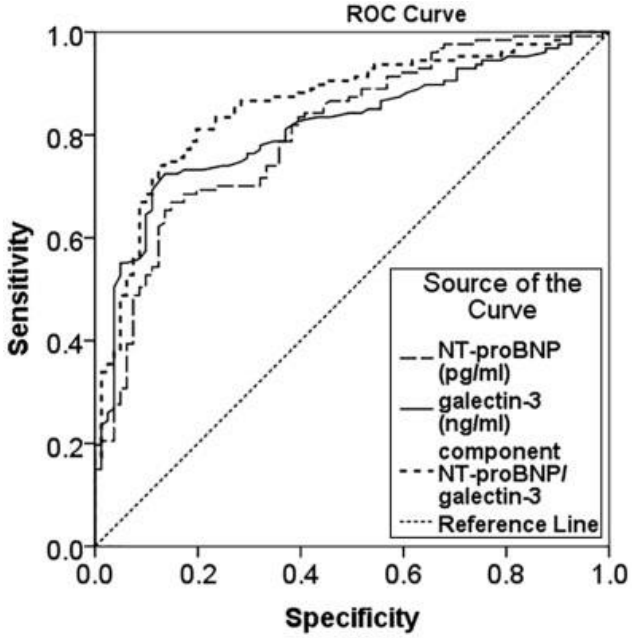


A base-10 log scale is used for the x- and y-axes. NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

Figure I.18. Pearson correlation between galectin-3 and NT-proBNP.

The diagnostic performance of both biomarkers was tested in all patients as well as in the subsets of patients with high risk and a potential for unclear interpretation of NT-proBNP and galectin-3. These subsets of patients were those with kidney failure (GFR of <60mL/minute/1.73m2), age of >60 years, obesity (BMI of >30 kg/m2), rhythm disorders (atrial fibrillation/flutter), LVEF of <40%, arterial hypertension, and type 2 diabetes mellitus. Patients with acute cardiac dyspnea showed significantly higher serum concentrations of both NT-proBNP and galectin-3 (Table I.25), both overall and in each particular subset of patients with these associated conditions ($p<0.05$ for all).

To test the diagnostic performance of NT-proBNP and galectin-3 for acute cardiac dyspnea, comparative accuracy was evaluated using ROC analysis. Both biomarkers showed similar diagnostic abilities as indicated by the lack of statistically significant differences between the AUCs (Table I.26). Dimension reduction through principal component analysis was used to ascertain whether the component summarizing both NT-proBNP and galectin-3 into a single latent variable may be of use in diagnostic prediction. Better predicting accuracy was found when using the component latent variable (AUC 0.859, $p<0.001$) than when using the two biomarkers independently (NTproBNP: AUC 0.807, $p<0.001$; galectin-3: AUC 0.815, $p<0.001$) (Figure I.19).



NT-proBNP, N-terminal prohormone of brain natriuretic peptide; ROC, receiver operating characteristic.

Figure I.19. ROC curves for the diagnosis of acute cardiac dyspnea for NT-proBNP, galectin-3, and the component of the two markers.

The diagnostic performance of the two biomarkers was also studied in subsets of particular interest, given the increased cardiovascular morbidity/mortality in the general population (age of >60 years, GFR of <60 mL/minute/1.73 m2, obesity as defined by a BMI of >30 kg/m2, impaired left ventricular function as defined by an LVEF of <40%, type 2 diabetes mellitus, and rhythm disorders). There were no statistically significant differences between the AUCs for galectin-3 and NT-proBNP in any of the high-risk subsets (Table I.26). ROC analysis also indicated that the optimal diagnostic cut-offs values were higher in certain high-risk subsets of patients such as those with impaired renal function, impaired cardiac function (reduced LVEF), rhythm disorders, and diabetes than in the overall study group (Table I.26).

Table I.26. Diagnostic test performance of NT-proBNP and galectin-3 for acute cardiac dyspnea.

Biomarker	AUC (95% CI)	p	Sensitivity (%)	Specificity (%)	Optimal cut-off	p
All patients						
NT-proBNP (pg/mL)	0.781 (0.718–0.835)	0.55	66.13	82.14	1538	0.000**
Galectin-3 (ng/mL)	0.803 (0.742–0.855)		72.6	84.52	18.8	0.000**
Age of >60 years						
NT-proBNP (pg/mL)	0.745 (0.675–0.807)	0.13	66.7	77.9	1538	0.000**
Galectin-3 (ng/mL)	0.811 (0.746–0.866)		75.7	83.8	18.8	0.000**
Obesity (BMI of >30 kg/m^2)						
NT-proBNP (pg/mL)	0.781 (0.659–0.875)	0.44	58.97	87.5	1081	0.000**
Galectin-3 (ng/mL)	0.841 (0.727–0.921)		74.36	91.67	19.5	0.000**
GFR of <60 mL/minute/1.73 m^2						
NT-proBNP (pg/mL)	0.671 (0.545–0.781)	0.28	75.0	60.0	1538	0.023*
Galectin-3 (ng/mL)	0.769 (0.650–0.863)		80.77	73.33	18.6	0.006*
LVEF of <40%						
NT-proBNP (pg/mL)	0.792 (0.597–0.921)	0.23	83.33	75	2065	0.071
Galectin-3 (ng/mL)	0.651 (0.449–0.820)		75	75	19.5	0.481
Rhythm disorder (atrial fibrillation/flutter)						
NT-proBNP (pg/mL)	0.697 (0.605–0.779)	0.07	51.06	86.36	3228	0.0007*
Galectin-3 (ng/mL)	0.825 (0.743–0.889)		71.28	90.91	17.9	0.000**
Type 2 diabetes mellitus						
NT-proBNP (pg/mL)	0.838 (0.719–0.921)	0.64	67.57	90.91	1648	0.000**
Galectin-3 (ng/mL)	0.803 (0.679–0.895)		75.68	81.82	18.5	0.000**

NT-proBNP, N-terminal prohormone of brain natriuretic peptide; AUC, area under the curve; CI, confidence interval; BMI, body mass index; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction. *p<0.05, **p<0.0001.

Discussion

Current guidelines recommend an active and rapid approach to establishing the diagnosis of acute heart failure; specific treatment should be promptly initiated within an optimal time frame of 30 to 60 minutes after admission (Mebazaa et al., 2015; Mebazaa et al., 2016; Ponikowski et al., 2016; Arrigo et al., 2016). In a "real life" context, patients with acute dyspnea and/or atypical manifestations of heart failure often require multidisciplinary evaluation by a cardiologist, pulmonologist, and internist, which is time-consuming and technically demanding, requiring chest X-ray and TTE and/or computed tomography pulmonary angiography.

This prospective observational study focused on the difficulties that confront the clinician when assessing dyspnea of acute onset. Furthermore, the heterogeneity of patients included in the present study with respect to the age range and different etiologies of heart failure as triggering factors of acute dyspnea reflects "real life" situations. Although easily

manageable by the primary care physician, a significant number of similar presentations in the ED are related to hypochondria and anxiety (Stephenson & Price, 2006).

Although BNP and NT-proBNP have an established position regarding their diagnostic abilities in acute heart failure (Class I recommendation), multiple interferences with different pathologies limit the utility of these biomarkers in emergency situations (Darche et al., 2017; Yancy et al., 2017). A significant proportion of the study group presented to the ED for aggravated dyspnea. This category of patients represents a major concern regarding a clinician's diagnostic abilities because chronic therapy tends to mask the signs and symptoms characteristic of acute heart failure.

An additional finding of this study is the paradoxical relationship between alcohol consumption and renal function. Higher estimated GFRs have been associated with chronic alcohol consumption. This paradoxical relationship can be partially explained by the diuretic effects of alcohol consumption through inhibition of vasopressin, but this finding requires cautious interpretation and judicious use in an adequate scientific context (Koning et al., 2015).

In this study, assessment of the serum concentrations of both NT-proBNP and galectin-3 showed significantly higher levels in patients with acute cardiac dyspnea, suggesting an ability to identify patients with increased cardiovascular risk. The same observation was true for subsets of patients with higher risk such as those with kidney failure, advanced age, obesity, rhythm disorders, impaired left ventricular function, arterial hypertension, and type 2 diabetes mellitus. While the values for both markers were higher in the deceased group than in the improved outcome group, galectin-3 had a tighter range than NT-proBNP in the deceased group. This may imply that galectin-3 has the potential to serve as a more specific prognostic factor.

The present study findings confirm that a significant association exists not only between NT-proBNP and acute cardiac dyspnea but also between galectin-3 and acute cardiac dyspnea. The existence of a strong correlation between NT-proBNP and galectin-3 lends credibility to the utility of a dual-biomarker approach to the diagnosis of acute cardiac dyspnea. High diagnostic accuracy for NT-proBNP and galectin-3 was demonstrated in the ROC analysis, indicating that both biomarkers are reliable tools for the prediction of acute cardiac dyspnea. The results were comparable when analyzing the entire study group as well as the subgroups of high-risk cardiovascular patients. After the independent analysis of the two biomarkers confirmed their diagnostic performance in identifying acute cardiac patients, a component variable was proven to have even better predictive diagnostic ability. This indicates that serum determination of galectin-3 enhances the diagnosis of acute cardiac dyspnea when used in conjunction with NT-proBNP.

Limitations were represented by a single tertiary center analysis, a limited number of patients, and the fact that the results are not applicable to pediatric patients or non-Caucasian ethnic groups.

Conclusions

A dual-biomarker analysis (NT-proBNP and galectin-3) represents an important practical approach that leads to early recognition of atypical manifestations of acute heart failure in patients with acute dyspnea presenting to the ED. The combination of NT-proBNP and galectin-3 is superior to NT-proBNP alone. These results have immediate clinical applicability in identifying high-risk cardiovascular patients who require intensive care treatment. Furthermore, accurate triage and early cardiovascular risk stratification of patients with acute dyspnea in emergency settings reduces the economic impact of the disease and associated treatments.

I.2. The complementary role of imagistic tests in diagnosis and outcome prediction

This direction of research is reflected in the following published articles:

1. **Lionte, C,** Sorodoc, V, Bologa, C, Tuchilus, C, Jaba, E. Usefulness of Transthoracic Echocardiography Parameters and Brain Natriuretic Peptide as Mortality Predictors in Hospitalized Acutely Poisoned Patients: A Prospective Observational Study. *Basic & Clin Pharmacol & Toxicol* 2017; 120 (5): 498-504. (**IF 2.659**)
2. Hriban AI, Crisu D, Ursaru M, Sorodoc L, **Lionte C**. An Uncommon Congenital Abnormality Discovered Using Multimodality Cardiac Imaging in an Elder Hospitalized for Decompensated Heart Failure. *Rom J Cardiol* 2021; 31 (3): 627-632. ISSN – online: 2734 – 6382. ISSN – print: 1220-658X
3. **Lionte C**, Bologa C, Petris Ovidiu, Sorodoc Victorita, Stoica Alexandra, Tuchilus Cristina, Jaba Elisabeta, Coman AE, Vata L, Haliga R, Sirbu O, Sorodoc L. Parameters influencing in-hospital mortality in acutely poisoned patients hospitalized in a medical or ICU ward: is there an influence of toxin-induced myocardial injury? *Rom J Cardiol* 2019; 29 (3): 404-410. ISSN – online: 2734 – 6382. ISSN – print: 1220-658X.
4. Haliga, RE, Sorodoc, V, **Lionte, C,** Petris, OR, Bologa, C, Coman, AE, Vata, LG, Puha, G, Dumitrescu, G, Sirbu, O, Stoica, A, Ceasovschih, A, Constantin, M, Catana, AN, Jaba, E, Sorodoc, L. Acute Clinical Syndromes and Suspicion of SARS-CoV-2 Infection: The Experience of a Single Romanian Center in the Early Pandemic Period. *Medicina-Lithuania* 2021; 57 (2): article number 121. DOI 10.3390/medicina57020121 **(IF 2.43)**
5. **Lionte C**, Bologa C, Şorodoc L. Toxin and drug-induced changes of the electrocardiogram. In: *Advances in Electrocardiograms - Clinical Applications.* PhD. Richard Millis (Ed.), InTech, 2012, pag. 271-296. ISBN 978-953-307-902-8
6. **Lionte C,** Sorodoc L, Petriş O, Sorodoc V. Electrocardiographic changes in acute organophosphate poisoning. *Rev Med Chir Soc Med Nat Iasi*. 2007;111(4):906-11. (ISSN: 0048-7848) PMID: 18389778

Background

Acute poisonings represent a common cause of morbidity and mortality worldwide (Krakowiak et al., 2011; Dart et al., 2015). Myocardial damage occurs after acute exposure to different xenobiotics, including drugs (i.e., antidepressants, antipsychotics, acetaminophen) (Hassanian-Moghaddam et al., 2014; Berling & Isbister, 2015; Ohtani et al., 1989), toxins (i.e., CO and pesticides) (Kao et al., 2009; Roth et al., 1993), drugs of abuse (i.e., methadone and cocaine) (Lusetti et al., 2016; Schwartz et al., 2010) or herbal toxin (i.e., aconite and wild mushrooms) (Tovar & Petzel, 2009; Unverir et al., 2007), and is a significant predictor of mortality in many of these situations (Hassanian-Moghaddam et al., 2014; Kao et al., 2009; Kim et al., 2014). Echocardiography alone, or combined with biomarkers, was used only in acute CO poisoning (Jung et al., 2014; Liu et al., 2014), and pesticide poisoning (Park et al., 2016; Lee et al., 2015) to assess cardiac toxicity. However, the utility of systematic TTE evaluation upon admission in a medical or ICU ward, with respect to the outcomes and mortality, was not performed in acutely poisoned patients. Furthermore, the combined analysis of troponin I with ECG and TTE parameters upon admission of an acutely poisoned patient in a medical or ICU ward, with respect to the outcomes and in-hospital mortality, was not performed.

Study regarding usefulness of transthoracic echocardiography in poisoned patients.

Aim of the research

The aim of this study was to analyze whether the cardiac function parameters assessed using TTE upon admission in the hospital, combined with brain natriuretic peptide (BNP), can be useful as early in-hospital mortality predictors in acutely poisoned patients with undifferentiated agents. The physician involved in the medical and intensive care of these patients could use these objective markers to identify immediately after admission the patients at risk of death, and adjust their management accordingly.

Materials and Methods

This prospective observational cohort study was performed in a referral center for Clinical Toxicology, from an 1128-bed university hospital, which includes an ED with over 85,000 visits annually, over a period of 12 months (October 2015–September 2016). We enrolled patients older than 18 years, irrespective of gender, which were addressed to the ED reportedly within 5 hours from poison exposure and admitted with suspected toxicity, confirmed after routine toxicological tests (serum level for ethanol, digitalis, carboxyhemoglobin, cholinesterase and urine toxicology screen) or gas chromatography–mass spectrometry analysis from initial sample, for other selected poisons. All subjects or their family (for unconscious patients) signed an informed consent prior to enrolment. The study was approved by the review board of the hospital and university and was conducted in accordance with the principles of the Helsinki Declaration and guidelines on Good Clinical Practice.

We included consecutive hospitalized patients with acute self-poisoning or acute unintentional poisoning. Offending agents were represented by: drugs (including prescription medication and OTC medicines), drugs of abuse, non-pharmaceutical agents (i.e., pesticides, chemicals, alcohols, herbal toxins), toxic gases or combination of multiple poisons. Patients without a signed informed consent, younger than 18 years, with an associated disease that can influence TTE pattern or BNP (i.e., diabetes, acute myocardial infarction or heart failure, chronic renal disease), patients with ocular/dermal exposures, with an acute pathology associated with poisoning (i.e., trauma, burns, including caustic burns, anaphylaxis etc.) or patients with incomplete data were excluded from our study.

All patients underwent routine assessment and management in the ED, which involved clinical examination, assessment of poisoning severity score, toxicological screen, complete blood count, arterial blood gases analysis, biochemistry profile (glucose, electrolytes, CK, renal and liver function tests), and measures of basic or advanced cardiac life support, decontamination, supportive and antidote therapy, where appropriate, and then were admitted to a medical or ICU ward. An ECG was recorded, and the venous blood was collected immediately after admission for routine laboratory tests and BNP analysis. The tests were repeated thereafter at the discretion of the attending physician, if it was necessary, for selected patients who developed complications. Brain natriuretic peptide was not reassessed before discharge. We used PATHFAST_ Cardiac Biomarker Analyzer (LSI Medience Corporation, Tokyo, Japan) for BNP detection. The cut-off limit of <100 pg/mL for BNP is recommended by the guidelines in the acute setting (Ponikowski et al., 2016).

We performed TTE in all poisoned patients, upon admission in the medical or ICU ward, to assess cardiac function, using a Fukuda Denshi Full Digital Ultrasound System UF-850XTD (Fukuda Denshi Co., Ltd., Tokyo, Japan). The following variables were calculated: left ventricle (LV) ejection fraction (EF), LV shortening fraction (SF), LV wall motion abnormalities (kinetics), E-wave deceleration time (EDT) of early LV diastolic filling, patterns of mitral diastolic filling (normal, abnormal relaxation, pseudonormal and restrictive filling),

the ratio of the early (E) to late (A) ventricular filling velocities (E/A), maximum aortic velocity (AoVmax) and inferior vena cava (IVC) diameters (inspiration–expiration). The parameters were collected and analyzed by the cardiologists in our team and their normal values were considered upon guidelines' recommendations (Lang et al., 2015; Lancellotti et al., 2015; Lancellotti & Cosins, 2016).

The patients were observed only during hospitalization. The main outcome measure was the status at hospital discharge. A favorable outcome was considered for patients discharged home with no symptoms, complications or disabilities, all complications being resolved during hospitalization. We considered as complications poison-induced rhabdomyolysis (CK > 1000 U/L), encephalopathy and seizures, acute respiratory failure requiring mechanical ventilation for more than 24 hr, arrhythmias with hemodynamic instability, acute myocardial injury (based on ECG pattern and increased troponin levels), acute liver injury (increased transaminase levels >10 times the upper normal limit with mild to moderate increased alkaline phosphatase levels), acute kidney injury (urine volume <0.5 mL/kg/h for 6 hours, based on Kidney Disease: Improving Global Outcomes criteria) and toxin-induced gastro-enteral lesions indicated by a superior or inferior digestive endoscopy (Chalasani et al, 2014; KDIGO, 2012; White & Hedge, 2007). A poor outcome was defined as in-hospital death.

Statistical analyses were performed with SPSS software for Windows (v.22.0; SPSS, Chicago, IL, USA). Nominal variables are presented as frequencies and percentages, and continuous variables are presented as mean ± standard deviation (SD) or median [25–75 percentiles] if not normally distributed. To identify significant parameters associated with poisoning-related fatalities, two-tailed Student's t-test was used to compare normally distributed continuous variables, the Mann–Whitney U-test was used to compare skewed data, and the Chi-square test and Cochrane's statistic were used for categorical variables. All significant variables in the univariate analyses for mortality were subjected to a multivariate logistic regression analysis. Risk was expressed as odds ratios (ORs) with confidence intervals (CI). Optimal cut points for the parameters analyzed were determined using the area under the curve (AUC) of the receiver-operating characteristic (ROC) with 95% CI and the associated p value representing the likelihood of the null hypothesis (AUC = 0.5). p values <0.05 were considered statistically significant.

Results

The patient screening and final study population are presented in Figure I.20. We analyzed 229 patients, with a mean age of 44.8 years (range 18–90 years), 50.7% women. Time to ED arrival was 3.2 ± 1.3 h (range, 0.5–5 h). The selected clinical characteristics (demographics, Glasgow Coma Scale score [GCS], poison types, vital signs, etc.) with respect to the outcome are included in table I.27. Age influenced significantly the mortality (Table I.27). The average initial GCS was 11 (range 3–15). The GCS below 8 was associated with a poor outcome in our patients (table I.27). The majority in our cohort were self-poisonings, and only 22 patients (9.6%) had an accidental exposure to a toxin. The poisons encountered in our cohort were as follows: 30.6% drug poisoning (sedative hypnotics in 25, antidepressants and cardiovascular drugs each in 14 patients, anti-epileptic in seven, antipsychotic in five, antimicrobials in three and antidementia agents in two patients); 29.4% combination of poisons; 13.5% pesticides (organophosphates in 21, carbamates in seven, rat poison in three patients); 8.7% toxic gases (CO and mixtures); 7.4% toxic alcohols and chemicals (ethylene glycol in seven, methanol in six, formaldehyde and hydrocarbon mixtures each in two patients); 6.1% OTC (NSAIDs in seven, acetaminophen in five and salicylates in two patients); 5.7%

illegal drugs (opiates in five, cannabis and ethnobotanicals each in three, and cocaine in two patients); 0.9% herbal toxins (wild mushrooms).

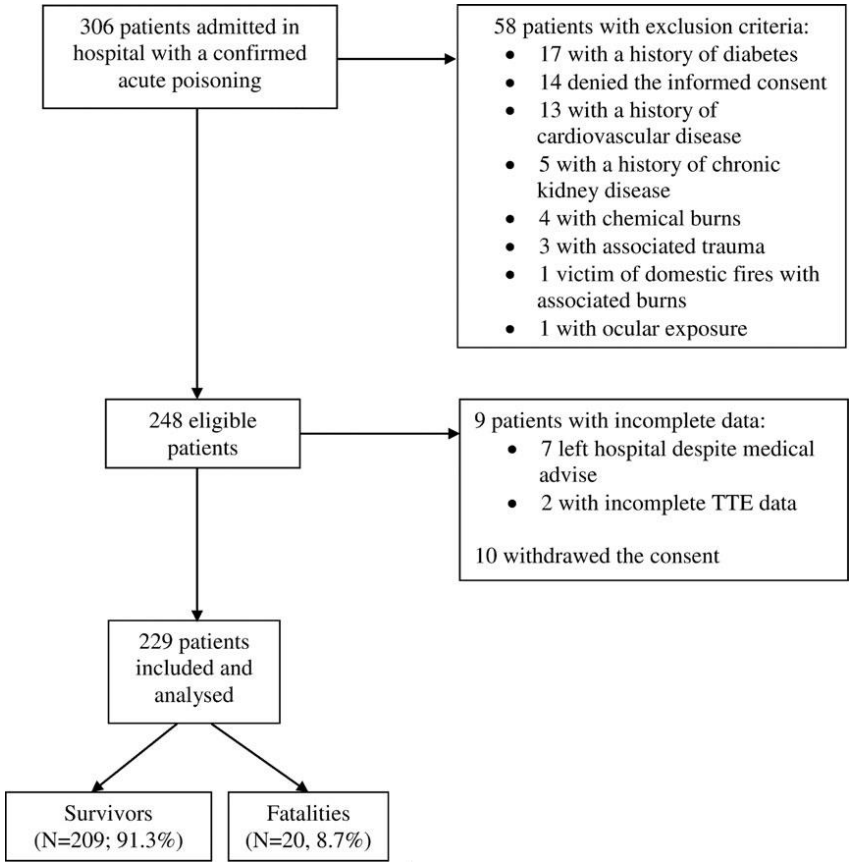


Figure I.20. Flow chart of patients included in the study and their outcome.

The mortality rate was higher in acute poisoning with non-pharmaceutical agents (Table I.27).

Table I.27. Selected characteristics of the patients with respect to the outcome.

Characteristics	Total (n = 220)	Survivors (n = 209)	Fatalities (n = 20)	*p* Value (survival *versus* dying)
Age (years)[1]	41 [33–59]	40 [32–56]	61.5 [57.5–73]	0.001
Gender; F (%)[2]	116 (50.7)	105 (45.9)	11 (4.8)	0.432
GCS score ≤8; n (%)[2]	45 (19.7)	36 (15.7)	9 (3.9)	0.006
Vital signs[1]				
HR (beats/min)	90 [75–106]	90 [75–105]	88 [68–112]	0.980
SBP (mmHg)	120 [110–140]	120 [110–140]	117.5 [80–136]	0.213
DBP (mmHg)	76 [70–80]	77 [70–80]	72 [50–83]	0.116
Poison type; n (%)[2]				0.010
Drugs	97 (42.4)	93 (40.6)	4 (1.7)	
Non-pharmaceutical agents	70 (30.6)	58 (25.3)	12 (5.3)	
Combination of poisons	62 (27.0)	58 (25.3)	4 (1.7)	
Ethanol co-ingestion (mg/dL)[1]	1 [1–30.5]	1 [1–30.5]	2 [1–43.8]	0.617
BNP (pg/mL)[1]	23.1 [6.0–81.0]	21.7 [5.0–67.0]	161.5 [74.5–317.5]	0.001
Abnormal ECG (%)[2]	57.2	50.0	7.2	0.035

[1]Data are presented as median [25–75 percentiles] and p value by Mann–Whitney U-test. [2] % within entire cohort and p value by Chi-square proportion test. GCS, Glasgow Coma Scale; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; OTC, over-the-counter; BNP, brain natriuretic peptide.

Sixty patients (26.2%) had ethanol co-ingestion, which had no influence on mortality. Vital signs were not substantially different within outcome groups. ECG was abnormal upon admission in 57.2% patients (table I.27).

The ECG abnormalities recorded were represented by arrhythmias (ranging from premature atrial or ventricular complexes to paroxysmal arrhythmias or asystole) in 85 (37.1%) patients, conduction disturbances (ranging from transient first-degree atrioventricular blocks to bundle branch blocks) in 15 (6.6%) patients, ST segment and T wave changes (ranging from negative T waves in two contiguous leads to ST segment elevation or depression with inverted T waves) in 31 (13.5%) patients.

Of the entire cohort, 116 patients (50.6%) developed complications (21.8% multiple complications involving more than two systems and organs, 10.9% cardiovascular, 5.2% central nervous system, liver complications and rhabdomyolysis 3.5% each, 3.1% respiratory, 1.7% renal and 0.9% gastrointestinal complications). Of the 229 patients, 20 patients died (8.7%) as a result of multiple complications. The average total number of days in the hospital was 4.5±3.6, significantly prolonged in non-survivors (7.1 ± 5.6 days versus 4.2 ± 3.2 days, p 0.001). Deaths were recorded in patients poisoned with toxic alcohols and chemicals (3.1%), prescription drugs (1.7%), combination of poisons (1.7%), toxic gases (1.3%) and organophosphate pesticides (0.9%).

Brain natriuretic peptide was notably increased in patients poisoned with toxic gases compared with patients intoxicated with combination of poisons (227.15 ± 314.62 versus 69.69 ± 164.51 pg/mL, p 0.02) and, respectively, with OTC poisoning (227.15 ± 314.62 versus 20.06 ± 23.33 pg/mL, p 0.024).

Among TTE parameters analyzed, we noticed that alteration in both diastolic and systolic LV function, along with the presence of LV regional or global wall kinetic abnormalities, had a significant impact on the mortality (table I.28).

Table I.28. Transthoracic echocardiography patterns in acute poisoning based on the outcome.

Parameter observed	Total (n = 229)	Survivors (n = 209)	Fatalities (n = 20)	*p* Value
LVEF (%)[1]	55 [50–60]	56 [51–60]	41.5 [39–50]	0.001
LVSF (%)[1]	28 [24–32]	28 [25–32]	20.5 [15–26]	0.001
EDT (ms)[1]	207 [179–233]	201 [178–226]	255 [236–267]	0.001
E/A ratio[1]	1.1 [0.8–1.5]	1.1 [0.9–1.5]	0.8 [0.7–0.9]	0.001
AoVmax (m/s)[1]	1.1 [1.0–1.3]	1.1 [1.0–1.3]	0.8 [0.7–1.0]	0.004
IVC diameter (mm)[1]	19 [17–20]	19 [17–20]	18 [16–22]	0.595
Abnormal LV Kinetics; n (%)[2]	58 (25.3)	44 (19.2)	14 (6.1)	0.001

[1]Data are presented as median [25–75 percentiles] and p value by Mann–Whitney U-test. [2] % within entire cohort and p value by Chi-square proportion test. DT, deceleration time; LVEF, left ventricle ejection fraction; LVSF, left ventricle shortening fraction, AoVmax, aortic maximal velocity; IVC, inferior vena cava; LV, left ventricle.

We also found a positive statistical correlation between the elevated BNP level (>100 pg/mL) and the prolongation of EDT (>220 ms) in all studied groups (p 0.034), also between BNP >100 pg/mL and a decreased left ventricle ejection fraction (LVEF) (<50%) in the cohort analyzed (p 0.001).

The LVEF was significantly lower in poisoning with toxic alcohols and chemicals (50.0 ± 10.5%), as compared with combination of poison exposures (54.3 ± 7.9%, p 0.05), prescription drug poisoning (54.9 ± 7.8%, p 0.026), pesticide exposures (54.9 ± 6.8%, p 0.043) and OTC intoxication (59 ± 6.3%, p 0.002). Also, compared with OTC poisoning, LVEF was significantly decreased in toxic gas exposure (51.9 ± 9.4%, p 0.011).

E-wave deceleration time was significantly prolonged in patients exposed to toxic alcohols and chemicals, as compared with patients with prescription drug poisoning (236.5 ± 33.7 versus 206.4 ± 46.7 ms, p 0.005), with pesticide poisoning (206.3 ± 39.4 ms, p 0.011), combination of poisons (201.9 ± 33.8 ms, p 0.001), with OTC poisoning (197.75 ± 42.7 ms, p 0.006), patients exposed to illicit drugs (189.1 ± 21.1 ms, p 0.001) and with vegetal poisons intoxication (166.5 ± 20.5 ms, p 0.017).

The IVC diameter was notably increased in patients with non-pharmaceutical agents acute poisoning, as opposed to patients with drug poisoning (19.34 ± 3.17 versus 18.04 ± 2.59 mm, p 0.025). The rest of the TTE parameters showed no significant differences among poison groups.

After univariate logistic regression analysis, several variables correlated with mortality, but only age, EDT and BNP showed a predictive value for mortality in acute poisoning after multivariate logistic regression analysis (table I.29).

Table I.29. Uni- and multi-variate logistic regression for variables associated with mortality.

	Univariate logistic regression			Multivariate logistic regression		
Variable	OR	95% CI	*p*	OR	95% CI	*p*
Age	3.441	1.985–5.964	0.001	2.658	1.226–5.762	0.013
GCS ≤8	0.254	0.098–0.658	0.005			
SBP	0.978	0.958–0.998	0.033			
DBP	0.951	0.920–0.984	0.004			
Abnormal ECG	0.281	0.077–1.022	0.054			
BNP	1.399	1.010–1.937	0.043	1.613	1.022–2.548	0.040
LVEF	0.247	0.143–0.427	0.001			
LVSF	0.182	0.085–0.388	0.001			
EDT	3.614	2.022–6.457	0.001	3.444	1.543–7.690	0.003
E/A ratio	0.128	0.034–0.444	0.001			
AoVmax	0.417	0.222–0.783	0.006			
LV Kinetics abnormalities	8.750	3.179–24.085	0.001			

OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; BNP, brain natriuretic peptide; LVEF, left ventricle ejection fraction; LVSF, left ventricle shortening fraction; EDT, E-wave deceleration time; AoVmax, aortic maximal velocity.

We observed all predictive variables, and these three demonstrated a good discriminatory power for mortality using ROC methodology (Figure I.21).

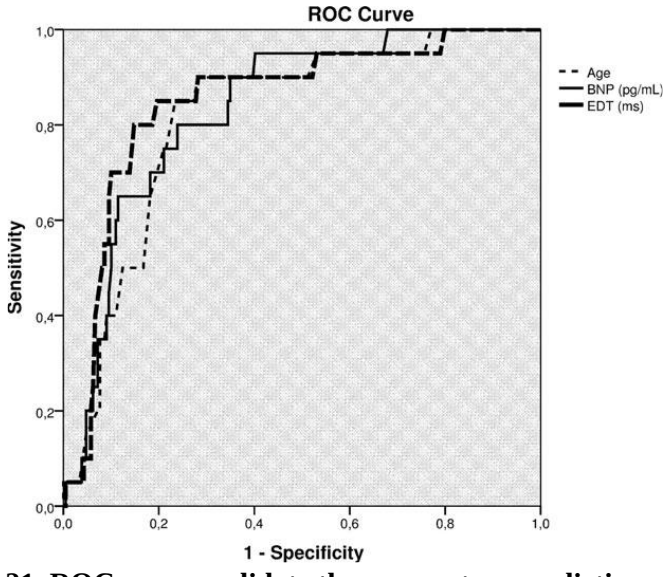


Figure I.21. ROC curves validate the parameters predicting mortality.

Areas under the curves were: EDT (E-wave deceleration time): 0.849 (95% confidence interval 0.762–0.936, p 0.001); BNP (brain natriuretic peptide): 0.832 (95% confidence interval 0.754–0.910, p 0.001); age: 0.819 (95% confidence interval 0.735–0.903, p 0.001). The following cut-off values were indicated corresponding to the minimal false-negative and false-positive results: BNP of 100 pg/mL with 65% sensitivity, 79% specificity, 31% positive predictive value (PPV), 96% negative predictive value (NPV); EDT of 220 ms with 90% sensitivity, 72% specificity, 24% PPV, 98% NPV. A BNP 80 pg/mL cutoff was also tested, which increased the sensitivity to 75%, but the PPV was lower, while specificity and NPV remained unchanged.

Discussion

This is the first study, to our knowledge, which prospectively analyzed the TTE parameters assessed systematically upon admission in a heterogeneous cohort of acutely poisoned patients presenting to the hospital within 5 hours of exposure and concomitantly correlated these parameters with clinical parameters, ECG and BNP. Despite a relatively small number of fatalities (20 patients, 8.7%), we observed an important relationship between alteration in LV function and BNP levels with the risk of mortality.

Our results showed, in accordance with those reported in herbicide poisoning (Kim et al., 2014), that age influenced in-hospital mortality of patients acutely poisoned with undifferentiated xenobiotics, as expected, because elderly might have a modified toxicokinetics or toxicodynamic of poisons, explained by associated comorbidities or changes in metabolic pathways.

Brain natriuretic peptide elevations are accurate in diagnosing diastolic dysfunction with the same effectiveness as in systolic dysfunction. Asymptomatic LV dysfunction alone leads to higher baseline BNP levels. As a general guideline, the cutoff point used in acute settings for BNP is less than 100 pg/mL (Ponikowski et al., 2016; Felker et al., 2006). A meta-analysis suggested that lower BNP thresholds may provide important prognostic information in different clinical settings, but data to clearly establish whether other BNP threshold provides an independent prediction of risk are lacking (Devereaux & Sessler 2015). NT-proBNP was proved to have a negative correlation with LVEF in patients acutely poisoned with CO (Liu et al., 2014). Our previous experience showed that biomarkers are indicators for the need of ICU admission, being correlated with early complications, and the short-term outcome (Lionte et al., 2017). Based on the assessment of acutely poisoned patients with heterogeneous agents upon admission, we proved that BNP is increased in non-survivors, and a BNP cut-off point of 100 pg/mL accurately discriminated between survival and death in acute poisoning, and conferred a risk of mortality 1.6 times increased. These results are important for the future studies, because we tried to minimize the possible role of confounding factors imposing the above-mentioned exclusion criteria in acutely poisoned cohort studied. The only interference could come from the age and gender, knowing that BNP levels are elevated in older patients and in women more than men (Felker et al., 2006); however, the most commonly used decision threshold for BNP remains 100 pg/mL irrespective of age or gender, as guidelines emphasized for the acute setting (Ponikowski et al., 2016; Felker et al., 2006). Also, we did not find a significant difference in this biomarker level within gender groups and age in patients acutely poisoned with heterogeneous agents. We consider that only the acute effect of the poison on the heart, either direct toxicity, or subsequent to metabolic alterations, explained the changes in BNP level, which was correlated with the presence of left ventricular dysfunction, and with death. Brain natriuretic peptide might be added to troponin, which was strongly associated with in-hospital mortality in a cohort of adults with acute drug overdoses (Manini et al., 2016), in the initial evaluation of a poisoned patient.

Evaluation of the cardiac structures by ultrasound can rapidly provide data that would be of great interest in managing poisoned patients. Items of particular interest in the ED investigation of an unstable patient include the assessment of the LV function and contractility, or markers of the patient's volume status, such as IVC diameter, and the response of these parameters to therapeutic maneuvers (Arntfield & Millington, 2012; Zengin et al., 2013). In several acute poisoning, such as those associated with shock (i.e., calcium-channel blocker overdose), or with severe volume depletion as a consequence of the poison (i.e., salicylate overdose), echocardiography could bring important information to refine the management of the poisoning (Gussow, 2014). The role for echocardiography in assessing a poisoned patient was proved in CO poisoning, where changes in diastolic function, preceding systolic function abnormalities (Çiftçi et al., 2013) or various patterns of LV systolic dysfunction were observed (Park et al., 2016), and showed a better accuracy, as opposed to ECG changes in detecting CO-induced cardiac damage (Davutoglu et al., 2006). The results obtained in this cohort of acutely poisoned patients showed that the assessment with TTE of cardiac function parameters, especially EDT >220 ms, as a measure of diastolic function of the LV, showed increased odds of mortality by 2.44 times in this setting. Considering that diastolic dysfunction is a feature that precedes systolic dysfunction, we believe that our observations regarding patients exposed to different poisons (with various mechanisms of action) are important, and prolonged EDT which positively correlates with BNP levels over 100 pg/mL truly reflects the poison-induced subclinical heart damage, even in the absence of ECG changes. Although several changes in systolic function were observed in the analyzed cohort, they failed to predict significantly the mortality. This may be explained by the relatively low prevalence of recognized cardiotoxic drugs (i.e., antidepressants) or cardiotoxins (i.e., CO) in our cohort. The mortality rates recorded on different poisoned groups are increased compared with those reported elsewhere (Dart et al., 2015; Mowry et al., 2013). An explanation could be the absence of specific antidotes for digitalis glycosides (i.e., digoxin immune Fab) and toxic alcohols (i.e., fomepizole) in our country.

To the best of our knowledge, this is the largest study to demonstrate prospectively the utility of echocardiography parameters combined with a conventional cardiovascular biomarker to early predict, upon hospital admission, the outcome for a patient with acute poisoning. The present investigation has several important clinical implications: there are some objective available tests, such as the BNP level, or the presence of a diastolic dysfunction assessed with TTE, that are good predictors of in-hospital mortality in non-diabetic heterogeneous acutely poisoned patients. This is important for daily practice, because there are circumstances when the serum poison levels are not readily available, a GCS score <8 failed to accurately predict the mortality, and identifying high-risk patients could improve the medical and intensive care in this setting.

Several limitations should be mentioned. Including patients from a single tertiary center in north-east Romania implies a possible selection bias in the population studied, although the epidemiological and toxicological data are consistent with those reported in the United States or Europe (Krakowiak et al., 2011; Dart et al., 2015). A larger sample was not available for this analysis given the constraints applied from the exclusion criteria, to avoid bias from comorbidities in the echocardiography and cardiovascular biomarkers analysis. We could not calibrate the influence of toxin serum concentration, and we failed to monitor all patients at least 30 days after the acute poisoning, although in some cases, reassessment after 1 month from the acute event proved that ETT parameters returned to normal range. Finally, these results do not apply to the excluded population. Future multicenter prospective studies are warranted to confirm and further explore the implications of systematic echocardiography and

biomarker assessment in every patient admitted with an acute poisoning in the hospital, and to assess the role of associated chronic pathologies in overdose risk and mortality.

Conclusions

TTE parameters such as EDT and LVEF, combined with BNP obtained upon hospital admission, can predict the in-hospital mortality of non-diabetic acutely poisoned adults. As echocardiography parameters are objective, can be obtained fast and are less invasive, and BNP is widely available and routinely used in ED for patients presenting with acute dyspnea, they can be successfully applied in everyday practice as part of the general approach of an acute poisoning, to improve the management of these poisonings and early address the worse outcome and mortality.

Study regarding imagistic parameters useful to evaluate toxin-induced myocardial injury.

Aim of the research

The aim of this study was to analyze if myocardial injury, assessed using troponin I (TnI) measured upon admission and 6 hours after presentation, ECG, as well as the parameters of cardiac function using TTE in a cohort with acute poisoning hospitalized in a medical or ICU ward can be useful as an early predictor for a poor outcome and in-hospital mortality in acutely poisoned patients with different xenobiotics. Thus, the practitioners could optimize the strategies to identify the poisoned patients with acute myocardial injury and adjust their management to improve the outcome of these patients.

Materials and methods

We performed a prospective observational study in a cohort of patients acutely poisoned with different xenobiotics, over a period of 18 months (October 2016– March 2018). We enrolled consecutive patients older than 18 years, which were addressed to the ED within 12 hours from poison exposure and admitted in a medical or ICU ward with a diagnosis of acute poisoning, after obtaining an informed consent. The study was partially funded by an internal research grant of the university, approved by the review board of the hospital and university.

Patients had either an accidental acute exposure, or a self-poisoning with pharmaceutical agents (prescription drugs and OTC medicines), illicit drugs, nonpharmaceutical agents (i.e., pesticides, rodenticides, chemicals, toxic alcohols), vegetal toxins, toxic gases, or a combination of multiple poisons. Patients without a signed informed consent, younger than 18 years of age, with an associated disease that can influence biomarkers, ECG or TTE pattern (i.e., diabetes, acute myocardial infarction or heart failure, chronic renal disease, severe liver disease), patients with an acute pathology associated to poisoning (i.e., trauma, burns, anaphylaxis etc.), or patients with incomplete data were excluded from our study.

Poisoning severity score (PSS) was determined in all patients using the classical grading system (Persson et al., 1998). The venous blood was collected immediately after admission for conventional laboratory tests and troponin I (TnI) analysis, 6 hours after the admission for TnI (6h-troponin), also during the hospital stay at the discretion of the attending physician, to assess acute myocardial injury, according to the European Society of Cardiology guidelines (Thygesen et al., 2018). Cardiovascular biomarkers were determined from the blood sample with PATHFAST® Cardiac Biomarker Analyser (LSI Medience Corporation, Japan), and with ARCHITECT c16000 clinical chemistry analyser (Abbott Laboratories, USA). A standard 12-lead ECG was recorded upon ED presentation using a CardioM Medica ECONet 12 channels electrocardiograph and repeated during hospitalization when needed. The QTc was

calculated using the Bazett formula (Chan et al., 2007) and was considered prolonged if greater than 440 milliseconds (ms). We performed immediately after admission a standard TTE in all poisoned patients, using a Fukuda Denshi Full Digital Ultrasound System UF-850XTD (Fukuda Denshi Co., Ltd., Japan). The parameters' normal values were considered upon guidelines' recommendations (Lang et al., 2015; Lancellotti et al., 2015). We observed as an outcome measure the status at hospital discharge. A poor outcome was defined as multiple complications or in-hospital death. Patients with a myocardial injury detected during hospitalization were programmed for a follow-up thirty days post-discharge, but unfortunately not all patients were compliant with this recommendation.

Statistical analysis

The categorical variables were expressed as numbers and percentages and compared using the Chi-square test. The continuous variables were expressed as medians with interquartile ranges (IQR) and compared with the Mann-Whitney test. The variables were compared in univariate analysis (survivors vs deceased patients). All significant variables in the univariate analyses for in-hospital mortality were subjected to a multivariate logistic regression analysis. Risk was expressed as odds-ratios (OR) with confidence intervals (CI). Goodness-of-fit for multivariate models was confirmed using the Hosmer and Lemeshow test. The receiver operating characteristic (ROC) methodology was used to analyze the discriminatory capacity of predictive variables. ROC analyses were expressed as curve plots and calculated area under the curve (AUC) with 95% CI and the associated p value representing the likelihood of the null hypothesis (AUC = 0.5); p values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS software for Windows (V.22.0; SPSS, Chicago, IL, USA).

Results

We analyzed 222 patients, with a median age of 43 years (range 18-91 years), 50.9% men. Time to ED a rival was 4.2 ± 1.8 hours (range 30 minutes-12 hours). The selected clinical characteristics (demographics, PSS, GCS, poison types, vital signs, etc.) with respect to mortality are included in Table I.30, and Figure I.22.

43 patients in our cohort were exposed to combinations of poisons (15.5%), 40 were exposed to non-pharmaceutical agents (14.4%), 33 patients were poisoned with sedative-hypnotics (11.9%), 31 cases were exposed to pesticides (11.2%), 16 patients to antidepressant/ antipsychotic medication (5.8%). There were 15 patients exposed to toxic gases, mainly carbon monoxide (5.4%), and 11 patients with cardiovascular drugs poisoning (4%). The rest of the cases were poisoning with OTC medication, or other prescription drugs (Figure I.22), and only 4 patients had vegetal toxins exposure (1.4%). There were no significant differences in the outcomes based on the poison involved. Ethanol co-ingestion had no influence on the outcome or death.

Although there was a significant statistical difference in the age, PSS, GCS score of survivors versus non-survivors, these variables did not predict in-hospital mortality after multivariate logistic regression. 169 patients of the entire cohort (76.2%) developed complications, while 35 patients had multiple complications, involving at least two major organs or systems, and cardiovascular complications were recorded in 15.76 % patients. Patients with a poor outcome didn't have a significantly prolonged hospitalization (Table I.30). Deaths were recorded in 10 patients (4.5%) in our cohort, as follows: 4 patients (1.8%) intoxicated with combinations of poisons, 3 patients exposed to toxic alcohols and chemicals (1.4%), one pesticide exposure, one toxic gas exposure, and one patient poisoned with antidepressants. The direct cause of death was represented by multiple complications

(dysrhythmias, toxic-induced myocardial injury, refractory shock, acute respiratory distress syndrome, and multiple organ failure).

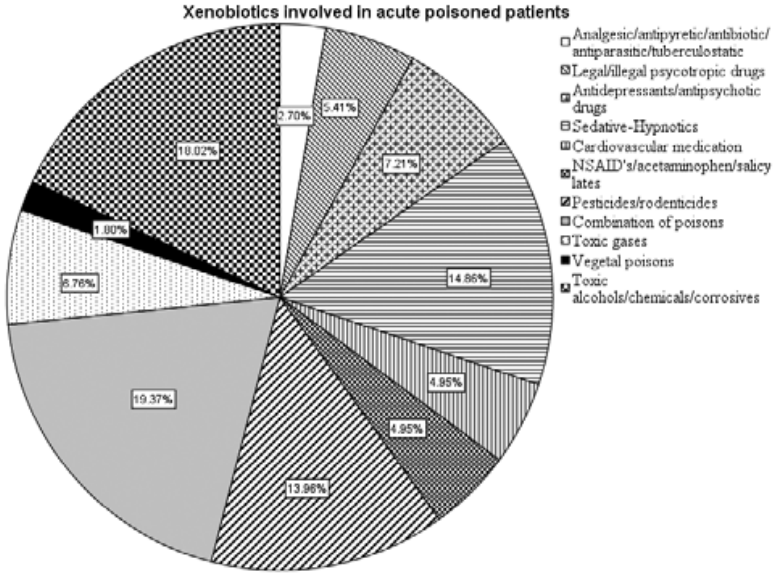


Figure I.22. Xenobiotics involved in acute poisoning in cohort studied.

Table I.30. Baseline characteristics of patients with acute poisoning according to survival.

Characteristics	**Total (n=222)**	**Survivors (n=212)**	**Non-survivors (n=10)**	P
Age[1] (years)	41 (31-56)	41 (30.25-54.75)	59 (54.50-69.50)	.003
Male gender[2] (%)	50.9	48.6	2.3	.953
Ethanol[1] (mg/dL)	1 (1-79)	1 (1-82)	1.5 (1-16)	.599
PSS[2] (%)				<.001
• Minor	35.2	35.2	0	
• Moderate	39.4	38.5	0.9	
• Severe	25.4	21.8	3.6	
Clinical signs (ED)				
• GCS[2] ≤ 8 (%)	11.3	9	2.3	.002
• HR[1] (bpm)	87 (73.75-100)	87 (75-100)	89.5 (57.75-107)	.754
• SBP[1] (mmHg)	120 (109.25-139)	120 (109.25-139)	120 (109.25-139)	.031
• DBP[1] (mmHg)	76 (67-83)	78 (70-83.5)	65 (40.5-81)	.053
Laboratory tests				
• Hemoglobin[1](g/dL)	13.70 (12.60-14.63)	13.70 (12.63-14.60)	13.95 (11.8-15.23)	.791
• pH[1]	7.40 (7.35-7.43)	7.40 (7.36-7.43)	7.04 (6.80-7.24)	<.001
• Creatinine[1](mg/dL)	.76 (.68-0.91)	.76 (.68-.88)	1.11 (.86-1.24)	.002
• ASAT[1] (U/L)	22 (17-37)	22 (17-35)	56.5 (30.5-93.5)	.001
• Myoglobin[1](ng/mL)	53.60 (36.70-107)	53 (35.95-90.45)	193 (46.71-542)	.008
Biomarkers				
• ED-TnI[1] (ng/mL)	.007 (.001-.050)	.006 (.001-.050)	.040 (.010-.050)	.055
• 6h-TnI[1] (ng/mL)	.002 (.001-.008)	.002 (.001-.006)	.101 (.014-1.004)	<.001
• ED-CKMB[1](ng/mL)	10 (1.55-22)	11 (1.50-22)	6.45 (3.84-23.96)	.849
Outcomes				
• Complications[2] (%)	47.2	37.98	9.52	<.001
• Hospitalization[1] (days)	3 (2-5)	3 (2-5)	2.5 (1.75-6.75)	.767

[1] Data are presented as median (25–75 percentiles) and p value by Mann-Whitney test; [2] % within entire cohort and p value by Chi square proportion test.

There was no significant statistical difference in TnI level within age and gender groups, while the mean initial levels of TnI were higher in non-survivor group (Table I.30) but didn't reach the statistical significance (p 0.55). Assessment of 6h-TnI showed a significantly higher value in the fatalities group (Table I.30).

When analyzing ECG, 40% subjects had an abnormal rhythm, while ST – T changes were seen in 36.8% patients and were predictive for a poor outcome (Table I.31).

Table I.31. Selected ECG and TTE parameters in acute poisoning based on the outcomes.

Parameter	Total (n=222)	Favorable outcome (n=187)	Poor outcome (n=35)	p value
ECG parameters				
Rhythm (%)				0.03
• Bradycardia	3.2	2.4	0.8	
• Normal rhythm	60	56	4	
• Tachycardia	31.2	23.2	8	
• Paroxysmal AF	5.6	4	1.6	
ST-T pattern (%)				0.07
• Normal	63.2	56	7.2	
• Inverted T waves	10.4	8.8	1.6	
• ST/T changes	16	10.4	5.6	
• ST elevation	10.4	9	1.4	
PR interval (s) [a,]*	0.16 (0.14-0.20)	0.16 (0.14-0.20)	0.16 (0.16-0.20)	0.302
QRS width (s)*	0.08 (0.08-0.10)	0.08 (0.08-0.10)	0.09 (0.08-0.11)	0.214
QTc interval (ms)*	423.99 (366.48-461.88)	421.64 (363.65-461.88)	472.95 (420.53-602.32)	.044
TTE parameters				
LVEF (%) [1]	56 (49.5-60)	56 (50-61)	40 (32.5-49)	<.001
LVSF (%) [1]	28 (24-32)	28 (25-32)	20 (14.5-24)	<.001
EDT (ms) [1]	210 (179-234)	207.5 (178.25-229)	256 (236-270.5)	.001
E/A ratio [a,1]	1.14 (0.86-1.53)	1.18 (0.89-1.55)	0.80 (0.72-1.00)	.006
Kinetics (%) [2]				<.001
• Global hypokinesia	23.2	14.4	8.8	
• Segmental hypokinesia	4.8	4	0.8	
• Normal kinetics	70.4	66.4	4	
• Hyperkinesia	1.6	0.8	0.8	

[1] Data are presented as median (25–75 percentiles) and p value by Mann-Whitney test; [2] % within entire cohort and p value by Chi square proportion test; [a,] 8 patients were excluded from this analysis because of paroxysmal AF; AF, atrial fibrillation; ECG, electrocardiogram; ST-T, ST segment and T wave; TTE, transthoracic echocardiography; DT, deceleration time of the E wave; LVEF, left ventricle ejection fraction; LVSF, left ventricle shortening fraction.

There were no significant differences in PR interval, QRS complex width within the outcome groups, however the QTc interval was significantly prolonged in patients with the poor outcome (Table I.31). There were no significant differences in the ECG parameters among poison groups.

At the time of the TTE, 8 subjects (3.6%) were in atrial fibrillation (Table I.31). Alteration in both diastolic and systolic LV function, along with presence of LV regional or global wall abnormalities had a significant impact on the outcome (Table I.31).

Logistic regression analysis

After univariate logistic regression analysis, age, the QTc interval, DT and 6h-TnI correlated with in-hospital mortality (Table I.32).

Table I.32. Univariate and multivariate logistic regression analysis for selected significant variables associated with mortality in acute poisoning.

Variable	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	p	OR	95% CI	p
Age	1.055	1.015-1.097	0.006	1.654	0.680-4.023	0.267
QTc interval	1.011	1.003-1.019	0.005	1.882	1.022-3.466	0.043
DT	1.026	1.009-1.043	0.002	3.653	1.460-9.137	0.006
6h-TnI	7.775	1.799-33.602	0.006	1.752	1.201-2.558	0.004

OR, odds ratio; CI, confidence interval; BNP, brain natriuretic peptide; DT, E wave deceleration time; 6h-TnI, troponin I detected 6 hours after the admission.

The multivariate logistic regression analysis including the same predictor variables showed that only the QTc interval (OR 1.882; CI 95%: 1.022-3.466; p 0.043), DT (OR 3.653; CI 95%:1.460-9.137; p 0.006) and 6h-TnI (OR 1.752; CI 95%: 1.201-2.558; p 0.004) are predictive for mortality in acute poisoning with different xenobiotics. The ROC analysis demonstrated two predictive variables to have a good discriminatory power for mortality (Figure I.23). Areas under the curves were: DT (E wave deceleration time): 0.801 (95% confidence interval 0.644-0.958, p 0.001); 6h-TnI (troponin detected 6 hours after admission): 0.889 (95 % confidence interval 0.789-0.990, p<0.001).

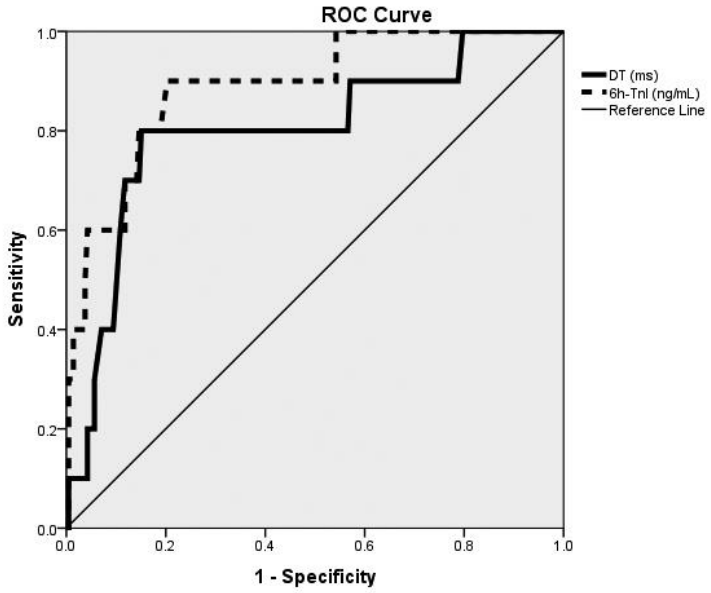


Figure I.23. Receiver Operating Characteristic Curves validates the discriminatory power of the parameters predicting mortality.

Discussion

This is the first study, to our knowledge, which prospectively and concomitantly correlates the TnI levels upon arrival and 6 hours after admission in a medical or ICU ward with ECG parameters and TTE indices in a heterogeneous cohort of acutely poisoned patients admitted to a medical or ICU ward within 12 hours of poison exposure. Despite a relatively small number of fatalities (10 patients, 4.5%), we observed a strong relationship between TnI dynamic, and alteration in LV function evaluated using TTE with the risk of a poor outcome and death.

ECG changes were analyzed in different poison exposures (Hassanian-Moghaddam et al., 2014; Kao et al., 2009; Cha et al., 2014; Akdur et al., 2010; Sanaei-Zadeh et al., 2013). Some studies demonstrated a correlation between the prolonged QT interval with cardiovascular events in patients with drug self-poisoning (Maignan et al., 2014), and with mortality, in herbicide poisoning (Kim et al., 2014). A QTc interval greater than 500 ms was predictive for cardiotoxicity in antipsychotic overdose (Khalaf et al., 2011) and, along with QT interval dispersion, was proved to be an independent predictor of adverse cardiovascular events in a heterogeneous cohort of 34 patients with suspected poisoning involving different types of drugs, alcohols, and herbal/OTC medication (Manini et al., 2010), also for cardiovascular complications in acute poisoning with cardiotoxic medication or poisons (Hassanian-Moghaddam et al., 2014). However, in methanol poisoning, abnormalities on the ECG suggestive for cardiotoxicity failed to predict mortality (Sanaei-Zadeh et al., 2013). Our results based on a larger cohort of poisoned patients, with acute exposure to heterogeneous xenobiotics, showed that the prolonged QTc interval >472 ms is correlated with a poor outcome and increases by 88% the odds of in-hospital mortality. This observation is important, because in our cohort, the proportion of agents proved to determine QTc prolongation and subsequent death (i.e., cardiovascular drugs, antidepressants, antipsychotics, pesticides) was 26.2%, the rest being poisons that were not associated until now with QTc interval prolongation-induced mortality. Also, it is consistent with our previous results on patients acutely poisoned with a systemic toxin (Lionte et al., 2017).

TnI is a biomarker with increased levels in pesticide poisoning (Cha et al, 2014; Lee et al., 2015), and a negative TnI on admission excludes fatality with an extremely high predictive value in undifferentiated patients with acute drug overdose (Manini et al., 2016). Our results showed that in acute poisoning with heterogeneous toxins, initial elevated TnI, but mainly elevation of 6-h TnI as a consequence of acute myocardial injury, is a biomarker predictive for a poor outcome and shows a 74% increased risk for in-hospital mortality in this setting. This is an interesting observation, mainly because we tried to include in our study patients without the comorbidities which could be associated with an increased troponin level (Petris et al., 2017). The possible mechanisms involved in acute poisoning complicated with myocardial injury might be the imbalance between the oxygen supply (decreased in CO exposure, after coronary vasospasm or toxin induced dysrhythmias or hypotension) and increased myocardial oxygen demands (in febrile patients such as neuroleptic poisoning, hypertension occurring in stimulants acute poisoning etc.), or as a consequence of direct myocardial cell death after inhibition of oxidative phosphorylation (Manini et al., 2016; Lionte et al., 2007; Lionte, 2010).

Echocardiography showed a better accuracy, as opposed to ECG changes, in detecting CO-induced cardiac damage, where changes in diastolic function, preceding systolic function abnormalities (Çiftçi et al., 2013), or various patterns of LV systolic dysfunction were observed (Çiftçi et al., 2013; Davutoglu et al., 2006; Park et al., 2016). Our previous experience with TTE in acute poisoned non-diabetic patients proved that assessment of diastolic function correlated with BNP level are useful to predict mortality (Lionte et al., 2017). The results obtained in this cohort of acutely poisoned patients showed that the assessment, using TTE upon admission in a medical or ICU ward, of cardiac function parameters, especially the diastolic function of the LV, accurately predicted the risk for a poor outcome and death in this setting, showing 2.65 times increased odds of mortality. We hypothesize that a prolonged DT may reflect the poison-induced subclinical heart damage, or the setting of acute myocardial injury, being recognized that diastolic dysfunction is a feature that precedes systolic dysfunction (Çiftçi et al., 2013; Davutoglu et al., 2006). Although several changes in systolic function were observed in the analyzed cohort, they failed to significantly correlate with in-

hospital mortality, possibly because of a relatively low prevalence of recognized cardiotoxins in our cohort.

To the best of our knowledge, this is the largest study to prospectively demonstrate the utility of troponin, combined with ECG and TTE parameters as markers of acute myocardial injury to predict, upon admission in a medical or ICU ward, the risk of a poor outcome and in-hospital death for acutely poisoned patients with different xenobiotics. The main limitation of the study may be that too few patients died during hospitalization to deliver reliable statistical data about in-hospital mortality. A larger sample was not available for this analysis given the constraints applied from the exclusion criteria, to avoid bias from co-morbidities in the cardiovascular biomarkers, ECG and echocardiography analysis. We could not calibrate the influence of toxin serum concentration, and we could not monitor all patients at least 30 days after the acute poisoning. Future prospective studies are warranted to confirm and further explore the implications of toxin-induced acute myocardial injury in every patient admitted with an acute poisoning in a medical or ICU ward.

Conclusions

In acutely poisoned adult patients, assessment of myocardial injury using initial and 6h-TnI, the QTc interval on initial ECG and the parameters of LV diastolic function obtained using TTE upon admission in a medical or ICU ward accurately predicted the outcomes and mortality. As TnI, ECG, and TTE are routinely used and not expensive, are less invasive, and are widely available, they can be successfully applied in everyday practice as part of the initial evaluation of acutely poisoned patients with different xenobiotics, to assess their outcomes. They may help hospital practitioners to improve the management of these poisonings and to early address the worst outcome and mortality.

I.3. Routine and new laboratory methods used in diagnostic evaluation of acutely poisoned patients

This direction of research is reflected in the following published articles:

1. Sorodoc L, **Lionte C,** Largu E, Petris OR. Benefits of butyrylcholinesterase reactivability testing in organophosphate poisoning. *Hum & Exp Toxicol* 2011; 30(11): 1769-1776. **(IF 1.772)**
2. Sorodoc, L.; **Lionte, C.;** Sorodoc, V.; Petris, OR; Badiu, C. Prolonged oral glucose tolerance test in nondiabetic patients with ethanol poisoning. *Acta Endocrinologica-Bucharest* 2009; 5(1): 61-73. **(IF 0.011)**
3. Sorodoc L, **Lionte C,** Largu E, Petriş O. New original in vitro method to assess cholinesterase reactivity in organophosphate poisoning. *Rev Med Chir Soc Med Nat Iasi* 2010;114(3):757-63. (ISSN: 0048-7848) **PMID:21235118.**
4. Bologa C, Rusu M, Ianovici N, Tetraru C, Hurjui J, Petriş O, **Lionte C**. [Role of calcium and magnesium ions in cerebrospinal fluid in alcoholic-traumatic coma]. *Rev Med Chir Soc Med Nat Iasi* 2003; 107(4): 809-812. (ISSN: 0048-7848). **PMID: 14756024.**

Study regarding new laboratory methods in organophosphate poisoning

Background

Organophosphate (OP) poisoning continues to be the leading cause of fatality among acute non-drug toxic pathologies, based on its high prevalence and its severity (Lionte & Sorodoc, 2005). Despite the existence of efficient antidotes, the prognosis in this type of

intoxication still remains reserved (Lionte et al., 2007). The diagnosis of acute OP poisoning is suggested by history and physical findings and confirmed by a depressed serum or red blood cells cholinesterase (acetylcholinesterase) level (Aaron, 2007). However, measurement of acetylcholinesterase is not a standard practice. By contrast, determination of plasma butyrylcholinesterase (BChE) is a routine test for monitoring the benefit of oxime antidote therapy in OP poisoning (Aurbek et al., 2009; Gradinariu & Petris, 2013; Naik et al., 2008). A limitation of this method results from the very wide interval of values for cholinesterase (ChEs) activity included in the range of normal. As a result, in medical practice, a relatively low value may represent the normal, while a so-called normal value may be detected when inhibition of the cholinesterase activity is present (Antonijevic & Stojiljkovic, 2007; Moss et al., 1986; Petris & Gradinariu, 2003; Worek et al., 2005).

Reversibility of cholinesterase inhibition after Toxogonin® (Tox) administration characterizes, with few exceptions, OP poisoning. The reactivation through Tox consists in the release of ChEs from the complex with OP, with the consequent regain of its enzymatic capabilities on choline compounds, expressed by an increase in the plasma cholinesterase (ChEs) values. Thus, in case of suspected OF poisoning, evaluation of reactivable ChEs activity will add important new perspectives for the diagnosis, compared with only the simple detection of the plasma ChEs activity. In a specific "in vitro" protocol of testing, adding Tox to the serum sample will generate a recovery of the ChEs activity only in circumstances of acute OF poisoning. ChEs activity will not be significantly influenced if there is no previous blockage of ChEs by OF. Tox-sensibilization method is based on the reactivation effect of Tox, which increases the level of ChEs activity when the enzyme is blocked by OF. This effect is possible only in the initial period after intoxication (generally the first 48-72 hours). Then, the enzyme becomes irreversibly blocked by OP, called "ageing process" (a dealkylation of the complex ChEs-OF). During this interval, obidoximes are efficient in recovering ChEs from their complexes with OP. This period can be longer, if the absorption still continues (i.e., additional ignored sites where absorption of poison persist, such as head hair, fat tissue, entero-enteric circuits etc.), or shorter, depending on the type of OP involved, the different ways the poisoning was produced etc. (Clark, 2002; Kassa et al., 2008; Richter et al., 2009). Another advantage of this test is the possibility to assess if the enzyme is still responsive to Tox, and sustains the continuation of Tox treatment, an expensive and even harmful treatment if the ChEs complex is “aged”; instead of unbinding the OF from the enzyme by linking with it, Tox will bind the enzyme, decreasing its level of activity even more (Petris et al., 2003). We described a protocol capable to evaluate the BChE activity level reactivation, which showed interesting perspectives for the diagnosis and optimization of antidote therapy compared with the simple detection of BChE level (Sorodoc et al., 2010).

Aim of the research

The aim of this study was to assess the usefulness of the currently used test of BChE activity, modified according to the protocol mentioned above, for the diagnosis and management of OP acute poisoning.

Materials and methods

Subject selection

In this study, serum samples from 23 consecutive patients, admitted with a diagnosis of OP acute poisoning in “Sf. Ioan” Emergency Clinic Hospital, Iasi (a regional Emergency Hospital which treats poisonings in North-East Romania and has a strong expertise in diagnosis and management of OP intoxications), over 1-year period were used. The inclusion criterion

was a diagnosis of acute OP poisoning in patients aged over 18. Exclusion criteria were: age less than 18, mixed poisonings, refusal of patient or patient's family to sign the informed consent, associated chronic therapies with ibuprofen, procainamide, phenazopyridine or L-Dopa, which are substances known to interfere with the spectrophotometric method of detection of the levels of activity of BChE used in the study (Young, 1990).

Method

In our hospital, the method used to determine the level of BChE activity is a colorimetric technique, using a Vitros System Chemistry 5,1/FS. In this method 11 mL drop of sample is evenly distributed on a dry, multilayered and analytical element coated type of slide. BChE brought in the reaction from the sample will hydrolyze butyrylthiocholine to thiocholine. The liberated thiocholine will reduce potassium hexacyanoferrate II. The rate of color loss is monitored by reflectance spectrophotometry (400 nm wavelength, multiple point rate test type) and is proportional to the amount of cholinesterase activity present in the sample. Reference interval is 4.65–10.44 U/ml (females) and 5.90–12.22 U/ml (males). The modified protocol (Sorodoc et al., 2010) was used to determine the level of BChE activity on 2 samples of 0.5 ml serum obtained from the same blood specimen. One sample was analyzed without any preparation, using the conventional method, and the second, after a preliminary incubation with Toxogonin®. The mixture was kept half an hour at 37°C on a water thermostat – to reproduce, at least at minimum, the conditions within the human body. We have diluted 0.5 ml Toxogonin® (from the 1 ml ampoule manufactured by Merck Pharma GmbH, containing as active ingredient obidoxime chloride, 250 mg/ml) with 4 and 5 ml NaCl 0.9%. Five micro liters of this 1/10 dilution contains 0.125 mg Toxogonin®. The blood samples were centrifuged immediately after collection. Serum was separated from the clot after centrifugation (technical specifications of the kit producer stating an interval of maximum 4 hours) and processed after a maximal period of 24 hours (the kit producer recommends a processing period of less than 7 days), while stored in refrigerator, at 2–8°C, never frozen (Champe & Harvey, 1987; Trundle & Marcial, 1988). The dilution was constituted at the moment of inclusion in the study for each patient, and used for all the tests of reactivation performed in that patient, at different moments during the week of monitoring. The prepared dilution was stored in a brown glass bottle (Sorodoc et al., 2010).

Every patient included in the study was evaluated in 14 different moments during the first week of hospitalization: upon admission, at three moments of the day (7 a.m., 3 p.m. and 11 p.m.) in the first 72 hours, and at 7 a.m. during the following 4 days. These relatively fixed moments were adopted in order to allow comparative analyses of the dynamic in reactivation of BChE. No modification was made in the therapeutic approach due to the study. Atropine therapeutic effect was defined by a heart rate of 90–110 beats/min, dry skin and mydriasis.

All aspects of the clinical study were in conformity with the bioethics rules endorsed by European Union legislation: Directive of the EU Council no. 609 from 24 November 1986, recommendations from the "Declaration of Helsinki"; recommendations from EU Directive 2001/20/CE, as well as the Romanian regulations for good clinical practice and clinical trials mentioned in Law 95/2006 (Chapter/Title "Medicine"), OMSP 904/28.07.2006, OMSP 906/28.07.2006. The study protocols have the approval of the Bioethics Commission of the "Grigore T.Popa" University of Medicine and Pharmacy Iasi and of the ''Sf. Ioan'' Emergency Clinic Hospital Iasi.

Statistical analysis

Comparisons of BChE levels of activity at each time between the two methods used were assessed with T-test (paired two samples for means). For all tests, p value less than 0.05

was considered significant. This statistical analysis was carried out using SPSS 17 (Statistical Package for the Social Sciences) software for Windows 7.0.

Results

We studied 23 consecutive patients poisoned with OP pesticides, 9 males aged 38.7 ± 17.4 and 14 females aged 39.6 ± 18.7. The toxin's entry route was digestive after ingestion in suicide attempt (20 patients) or after involuntary ingestion (3 patients). The quantity of ingested toxin was difficult to estimate in all patients, caused by lack of accurate information provided by patients, patient's families or Emergency Medical Services personnel. We have approximated that the amount of toxin involved was between a minimum of 15 ml and a maximum of 400 ml. We have confirmation about the specific OP involved in just three cases and these were Neguvon (two subjects) and Furadan (one subject). Demographic, clinical parameters and outcome of patients included in the study are represented in Table I.33.

Table I.33. Demographic, clinical symptoms and outcome of patients included in study.

No. subjects	Age (years)	Gender (M/F)	Provenience (rural/urban)	Type of poisoning (suicide/accidental)	Route of poisoning	Time to hospital admission (min)	Muscarinic symptoms	Nicotinic symptoms	Outcome (deaths/ survivals)
23	39.2 ± 17.6	9/14	17/6	20/3 (subjects G, N, H)	Ingestion	99 ± 85	23	19	1/22

All patients presented moderate or severe types of toxicity based on clinical signs and symptoms. Diagnosis of acute OP poisoning was suggested by history and physical exam, and confirmed by a decreased level of BChE activity, as well as by a positive atropine tolerance test. Evolution of the BChE reactivation assessed by 7 days monitoring of BChE levels of activity (determined using the conventional method and the Toxogonin® sensitized protocol) is presented in Table I.34 and Figures I.24 and I.25.

All patients were treated with aggressive supportive care and antidotal therapy with a favorable outcome in 22 of 23 subjects and were discharged from the hospital after 8.5 ± 2.3 days. The deceased patient (subject T) was a 43-year-old male with a history of severe ethylic psychiatric disorder and liver cirrhosis presenting at admission in the hospital with a profound coma (Glasgow Coma Score 5) and aspiration bronchopneumonia.

Discussion

The toxic mechanism of OP is based on their interaction and irreversible inhibition of acetylcholinesterase, BChE, carboxylesterases etc. by phosphorylation and phosphonylation of their active site serine. Inhibition of acetylcholinesterase is responsible for the characteristic symptoms of OP poisoning (Aurbek et al., 2009; Petris et al., 2009). Therapeutic strategies are directed to competitively antagonize overstimulation of muscarinic receptors by atropine, and to reverse ChEs inhibition by reactivation with oximes such as obidoxime and pralidoxime. Oximes should be administered in appropriate dosage as early as possible and effective concentrations should be maintained as long as the reactivation is possible (Thiermann et al., 2007). Despite the reluctance of some researchers towards the usefulness of serum BChE for kinetic analysis in OP intoxications, it is largely accepted for the practical utility of a correct identification of cholinesterases' behavior regarding oximes therapy, both in human and in experimental studies (Aurbek et al., 2009; Karasova et al., 2008). In this view, efforts for conceiving new protocols on ChEs through obidoxime-induced reactivation testing are reasonable to be undertaken and they will have practical value, if they consist in affordable modifications to an already existing laboratory methodology. This is especially the case of

developing countries, where investments in new medical technologies are not always easy to afford, these countries also being those where the prevalence of OP intoxication is the highest.

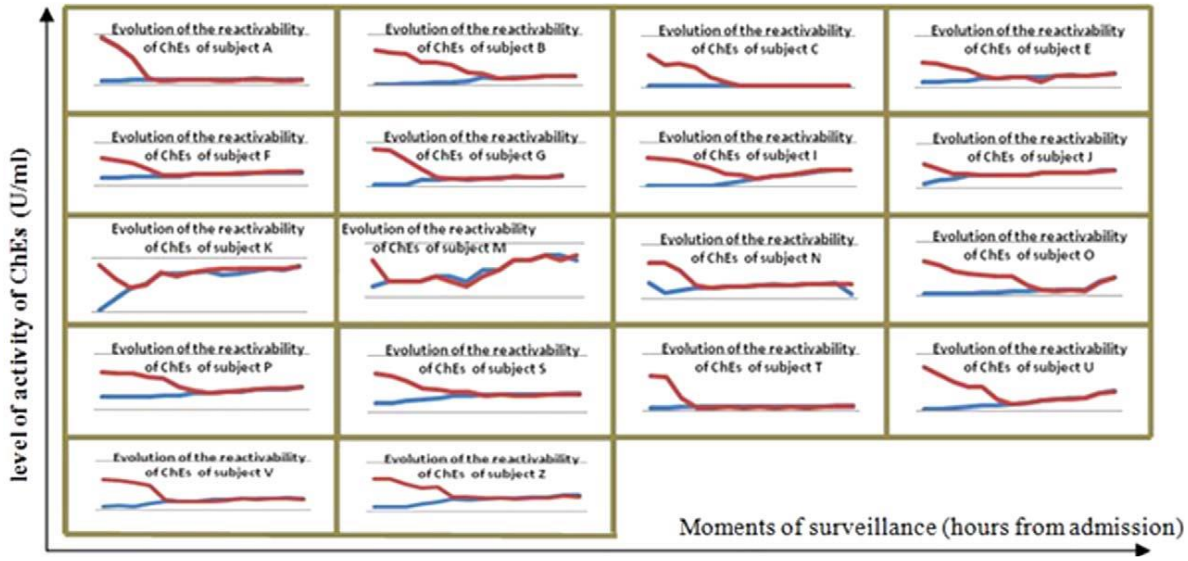
Table I.34. Evolution of the reactivation of cholinesterase (ChEs).

		Test: level of activity of ChEs (U/ml)																					
Moment of surveillance		A**	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	R	S	T	U	V	X	Z
Admission	Cm	0.4	0.2	0.3	0.3	1.1	2.1	0.2	1.3	0.2	1.1	0.2	1.2	0.2	0.9	0.2	2.2	0.3	1.7	0.2	0.2	0.4	1.1	0.9
	Tm	4.7	6.9	6.5	0.4	5	6.5	4.4	1.4	6.7	5.6	4.4	1.3	0.7	6.7	3.2	6.7	0.5	6.9	3.1	7.8	3.2	1.2	6.7
p Value		–	–	–	ns	–	–	–	ns	–	–	–	ns	ns	–	–	–	ns	–	–	–	–	ns	–
First 8 h	Cm	0.4	0.2	0.4	0.4	1.1	2	0.3	1.4	0.3	1.9	1.2	1.5	0.3	1.1	0.2	2.2	0.3	1.7	0.2	0.3	0.5	1.3	0.9
	Tm	3.9	6.4	4.6	0.4	4.8	5.9	4.3	1.4	6.5	4.4	3.1	1.4	0.3	6.8	2.9	6.4	0.5	6.5	3	6.5	3.1	1.4	6.6
p Value		–	–	–	ns	–	–	–	ns	–	ns	ns	ns	ns	–	–	–	ns	–	0.011	–	–	ns	–
First 16 h	Cm	0.5	0.4	0.4	0.4	1.4	2.2	0.3	1.2	0.3	2.3	2.1	1.6	0.3	1.5	0.2	2.3	0.5	2.1	0.3	0.4	0.4	1.3	1
	Tm	2.7	6.1	4.7	0.4	4	5.3	4.1	1.3	6.1	3.5	2.3	1.3	0.3	5.3	2.3	6.4	0.5	5.7	1.2	5.1	2.9	1.3	5.7
p Value		0.032	–	–	ns	–	–	–	ns	–	ns	ns	ns	ns	0.015	–	–	ns	–	ns	–	–	ns	–
First 24 h	Cm	0.5	0.5	0.5	0.5	1.4	2.3	0.3	1.6	0.3	3.1	2.6	1.8	0.3	1.9	0.2	2.3	0.7	2.3	0.3	0.7	0.7	1.7	1.6
	Tm	0.6	4.5	4.1	0.5	3.6	3.9	3.1	1.7	5.4	3.3	2.5	1.7	0.3	2.4	2.1	5.9	0.7	4.3	0.3	4.3	2.6	1.6	4.9
p Value		ns	–	–	ns	–	0.013	–	ns	–	ns	ns	ns	ns	0.049	–	–	ns	–	ns	–	0.001	ns	–
First 32 h	Cm	0.5	0.7	0.4	0.8	1.9	2.3	0.8	1.7	0.3	3.1	3.5	1.7	0.4	2.1	0.3	2.5	0.9	2.5	0.4	0.8	0.9	1.9	1.9
	Tm	0.4	4.4	2.1	0.8	2.3	2.3	2	1.7	4.5	3.1	3.7	1.8	0.4	2	2	5.7	0.9	4.1	0.3	4.2	1.1	2	5
p Value		ns	–	–	ns	0.015	ns	–	ns	–	ns	ns	ns	ns	ns	–	–	ns	–	ns	–	ns	ns	–
First 40 h	Cm	0.5	0.7	0.4	1.1	1.9	2.3	0.8	2.5	0.8	3.1	3.5	2	0.4	2.3	0.3	2.5	1.4	2.9	0.4	0.9	0.9	2.2	2.5
	Tm	0.5	4.1	1.1	1.1	1.8	2.3	1.1	2.4	2.9	3.1	3.4	2.1	0.3	2.2	1.9	4.1	1.3	3.7	0.4	2.1	0.9	2.2	3.2
p Value		ns	–	0.007	ns	Ns	ns	0.009	ns	–	ns	ns	ns	ns	ns	–	–	ns	–	ns	0.0047	ns	ns	–
First 48 h	Cm	0.6	0.9	0.4	1.1	2.1	2.7	0.9	2.7	1.3	3.2	3.6	2.2	0.3	2.2	0.4	2.9	1.2	2.9	0.4	1	0.9	2.2	2.4
	Tm	0.5	2.7	0.5	1.1	2	2.6	0.9	2.6	2.6	3.1	3.7	2.1	0.2	2.2	1.8	3.4	1.3	3.6	0.3	1.1	0.9	2.1	3.1
p Value		ns	0.0005	ns	ns	Ns	ns	ns	ns	0.001	ns	ns	ns	ns	ns	–	0.0015	ns	0.0089	ns	ns	ns	ns	–
First 56 h	Cm	0.5	1.7	0.4	1.4	2.1	2.7	0.8	2.9	1.9	3.2	3.8	2.5	0.5	2.5	0.4	2.9	1.6	3.1	0.4	1.4	1.1	2.5	2.6
	Tm	0.5	2.4	0.5	1.4	2.1	2.7	0.9	2.8	1.8	3.2	3.9	2.3	0.4	2.4	1.1	3	1.5	3	0.4	1.3	0.9	2.4	3
p Value		ns	ns	ns	ns	Ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	0.0001	ns	ns	ns	ns	ns	ns	ns	–
First 64 h	Cm	0.6	1.5	0.5	1.5	2	2.8	0.9	3.1	2.6	3.6	3.4	2.8	0.5	2.6	0.5	3.1	1.9	3.2	0.4	1.7	1.1	2.5	2.7
	Tm	0.4	1.4	0.4	1.6	1.1	2.7	0.9	3	2.5	3.6	4.1	2.8	0.5	2.4	0.6	3.2	1.7	3.2	0.3	1.8	1	2.4	3
p Value		ns	ns	ns	ns	Ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	0.007
First 72 h	Cm	0.5	1.6	0.4	2.1	2.3	2.8	1	3.4	2.8	3.5	3.5	2.8	0.7	2.5	0.6	3.3	1.9	3.1	0.4	1.9	1.2	2.5	2.7
	Tm	0.5	1.4	0.5	2.1	2.3	2.8	0.9	3.5	2.7	3.6	4	2.9	0.7	2.5	0.5	3.4	1.9	3	0.4	2	1.2	2.4	2.7
p Value		ns	ns	ns	ns	Ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
First 96 h	Cm	0.7	1.6	0.5	2.6	2.5	3	1.1	4	3.1	3.7	3.7	2.9	0.7	2.7	0.6	3.7	2.1	3.2	0.4	2.3	1.2	2.6	2.9
	Tm	0.5	1.6	0.4	2.6	2.4	2.9	1.2	4.3	3.2	3.7	4.1	3.5	0.7	2.6	0.6	3.6	1.9	3.1	0.3	2	1.1	2.5	3
p Value		ns	ns	ns	ns	Ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
First 120 h	Cm	0.6	1.9	0.5	3.1	2.4	3.1	1	4	3.6	3.7	4	3.4	0.8	2.7	0.6	3.8	2	3.1	0.4	2.3	1.2	2.6	3
	Tm	0.5	1.8	0.5	3	2.4	3.2	1	4.1	3.7	3.7	4	3.5	0.8	2.6	0.5	3.8	2	3.2	0.4	2.2	1.2	2.6	2.9
p Value		ns	ns	ns	ns	Ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
First 144 h	Cm	0.5	1.9	0.4	3.4	2.5	3.1	1.1	4.1	3.9	4.2	3.9	3.5	0.8	2.9	1.4	3.8	2.1	3.3	0.5	3.1	1.3	2.7	3.4
	Tm	0.4	1.9	0.4	3.4	2.5	3.1	1	4.1	3.9	4	4	3.4	0.7	2.7	1.3	3.8	2.1	3.2	0.4	3	1.2	2.6	3.3
p Value		ns	ns	ns	ns	Ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
First 168 h	Cm	0.6	1.8	0.5	3.8	2.8	3.1	1.3	4.2	3.8	4.2	4.2	3.7	0.7	2.9	1.7	4.2	2.1	3.4	0.5	3.6	1.2	2.6	3.3
	Tm	0.5	1.9	0.5	3.8	2.8	3.2	1.2	4.3	3.9	4.2	4.3	3.6	0.8	2.8	1.7	4.1	2	3.2	0.4	3.4	1.1	2.5	3.2
p Value		ns	ns	ns	ns	Ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

Cm, conventional method; Tm, Tox-serum incubation method; ns, without statistical significance. [a] Letters A to Z were assigned to the patients at the inclusion in the study.

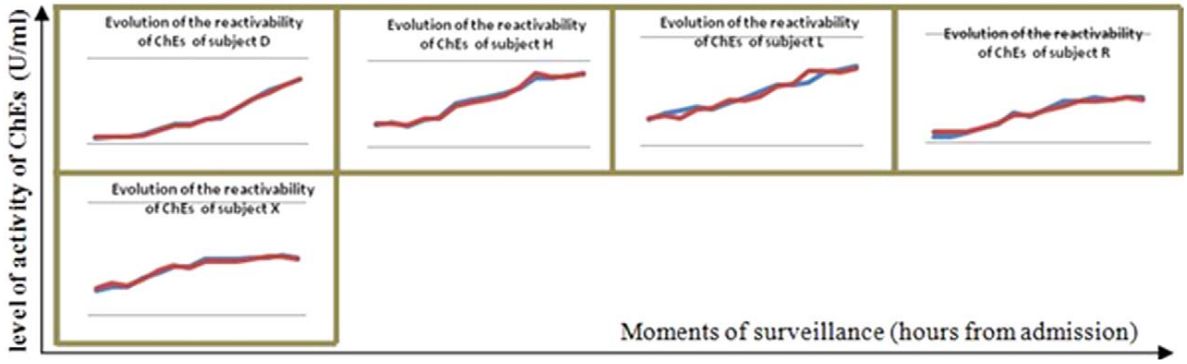
In diagnosing OP poisoning, the most frequently utilized laboratory test remains the quantitative assessment of BChE activity through its effect on butyrylthiocholine as substrate, using a colorimetric evaluation. Toxogonin®-sensitized method is based on the reactivation effect of Toxogonin®, which increases the level of ChEs activity, when OP blocks the enzyme. According to the literature, this effect is possible only in the initial period after intoxication (Petris et al., 2009; Thiermann et al., 2007). Shortly after, OP blocks irreversibly the enzyme, through an "ageing process", a dealkylation of the complex cholinesterase – organophosphate. During this interval, generally the first 48–72 hours after intoxication, obidoximes are efficient in recovering cholinesterases from their complexes with OP. This period could be longer if the absorption still continues – i.e., additional ignored sites where absorption of poison continues (head hair, fat tissue, entero-enteric circuits, etc.) – or shorter (depending on the type of involved organophosphate, modalities in which the poisoning was produced, etc.) (Clark, 2002; Kassa et al., 2008; Richter et al., 2009). An advantage of this test is the possibility to differentiate if the enzyme is still responsive or not to Toxogonin® and constitutes a justification for the continuation of Toxogonin® treatment, an expensive and even harmful one if the cholinesterases' complex is "aged". Instead of unbinding the OP from the enzyme by

linking with it, Toxogonin® will bind the enzyme, decreasing even more its level of activity (Petris et al., 2003).



Reactivation of BChE revealed a funnel-like pattern: upper red line – the results for the level of activity of cholinesterase (ChEs) obtained with the Tox-serum incubation method; lower blue line – the results for the level of activity of ChEs obtained using the conventional method).

Figure I.24. Evolution of butyrylcholinesterase (BChE) reactivability.

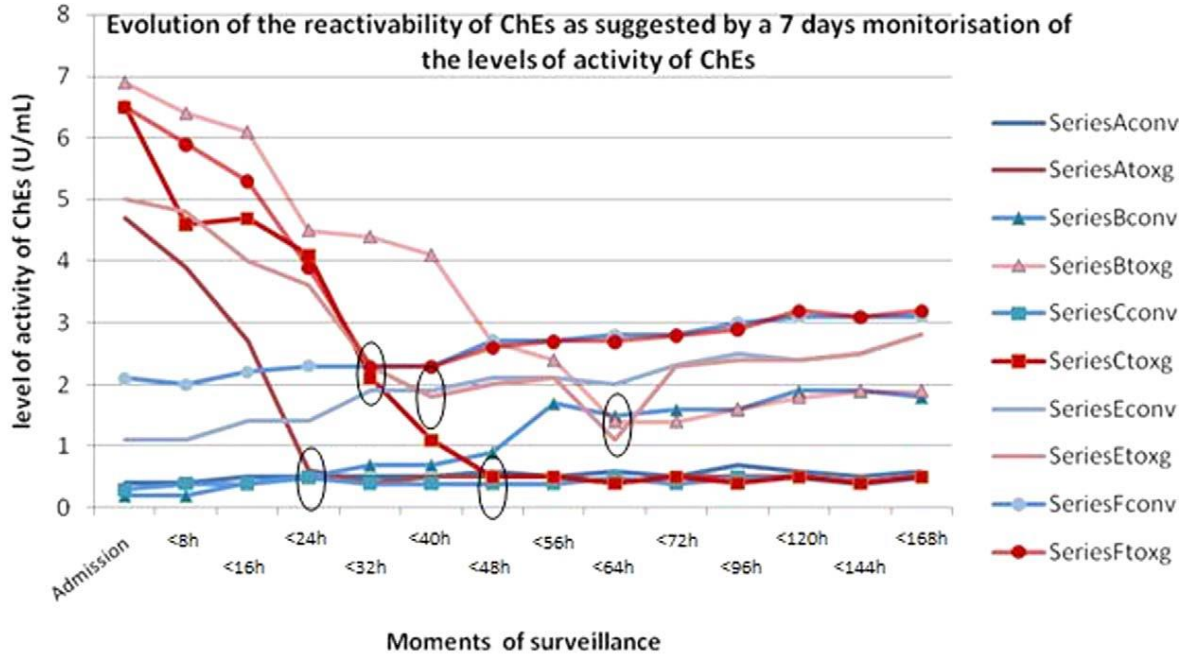


Absence of the funnel-like pattern - first red line: the results for the level of activity of cholinesterase (ChEs) obtained with the Tox-serum incubation method; second blue line: the results for the level of activity of ChEs obtained using the conventional method.

Figure I.25. Lack of Tox-induced butyrylcholinesterase (BChE) reactivability.

We consider as a strong aspect of our research the fact that we have tested a protocol easy to implement in the majority of medical emergencies institutions, being based on a method that is already widely used. Our research was a prospective, randomized clinical study undertaken on serum from human subjects, intoxication being caused by OP agents closer to day-to-day reality, not by nerve agents OP. Even if OP was not clearly identified in all the cases, they all belong to the common group used as pesticides, which are more currently involved, as individual poisonings, in the pathologies of an emergency department. Also, another strong aspect is the fact that the research did not use BChE after being frozen (at minus 80°C), as the technical specification of the kit producer clearly underlines. Studying the evolution of the reactivation of BChE, we have established, in 18 from 23 cases of OP poisoning, a pattern with the aspect of a funnel, consequence of the initial possibility to

increment the degree of BChE activity, due to Toxogonin® reactivation's effect (Figure I.24). Statistical analysis showed that in 15 of 18 cases with this pattern of reactivation of BChE, data obtained were significant ($p < 0.05$) as shown in Table I.34. Although the graphic image has the funnel pattern, in 3 cases (patients J, K and M) results did not achieve statistical significance (Table I.34), because these patients had a delay of more than 12 hours after poison ingestion to the moment of admission in hospital. This funnel shape defines the presence of reactivation and its absence, in 5 from the total of 23 studied cases, a lack of effect of Toxogonin® due to BChE ageing process (Figure I.25). The isthmus of the funnel shape indicates from which point further BChE is no longer reactivable through Toxogonin®. As observed in Figure I.26 (representing, due to considerations of visibility in the graphic, only the subjects – A, B, C, E and F), the loss of BChE Toxogonin®-induced reactivation does not appear in a predetermined moment of the intoxication. For all 23 subjects included in study, the documented extremes were the first 8 hours in subject M versus 64 hours in subject Z.



Graphic representation of cases A, B, C, E and F (marked with circles are the defined "isthmus of the funnel-like pattern" which represent the moment in the evolution of the OP intoxication when the reactivation is no longer efficient).

Figure I.26. Evolution of the reactivation of BChE activity.

Thus, this important moment in the evolution of the OP poisoning cannot be predicted other than by monitoring the subjects with the Toxogonin®-sensitized method. Due to the necessity for an easiness of application and a clear study design, the graphical representation in Figure I.26 used as starting point the moment of admission and not the moment of intoxication, as it has been more scientifically rigorous. Despite this, the conclusion stated was not significantly affected because the general influence of time between ingestion and the admission to hospital was minimal (Table I.33) in the series of cases studied.

Conclusion

In case of a suspected OP poisoning, an important new perspective to the diagnostic evaluation and management of antidote therapy appears to be assessment of BChE reactivation, as compared with only the simple detection of the BChE activity. In a specific "in vitro" testing protocol, adding Toxogonin® to the serum sample will generate a recovery of the BChE

activity in circumstances of acute OP poisoning. A Toxogonin®-induced reactivation of BChE activity, highlighted with an "in vitro" test will add more trust to the practitioner that he is facing the correct diagnosis and will have the potential for a better quantification of the severity, and prognosis for this toxic situation. Analyzing "in vitro" the effect of Toxogonin® on restoring the level of BChE activity resulted in a safe, non-expensive, easy-to-perform, quick (<1 hour) test capable to offer new, interesting perspectives on organophosphate intoxications.

Study regarding routine laboratory methods in ethanol poisoning

Background

Ethanol is the most widely used recreational drug in Western industrialized countries. There is a large body of medical literature examining the effect of alcohol on carbohydrate metabolism in healthy, nondiabetic individuals, as well as in diabetics (Van de Wiel, 2004; Lionte et al., 2003; Lionte & Hurjui, 2003). Alcohol ingestion can induce either a hyperglycemia, or a hypoglycemia. The hyperglycemic effect appears when there are enough quantities of glycogen in the liver and is directly related with the amount of alcohol ingested (Lionte, 2004). Alcohol may improve insulin sensitivity when consumed in small amounts. At higher levels of intake, alcohol may interfere with insulin mediated glucose disposal, causing insulin resistance (Parrott, 2002). Alcohol consumption, which has a large prevalence in general population, represents one of the most frequent causes of hypoglycemia. This can occur not only in chronic alcoholics, but also in occasional consumers (Lionte, 2004). Alcohol dehydrogenase and aldehyde dehydrogenase metabolize alcohol to acetaldehyde and subsequently to acetic acid in the mitochondria. This process leads to the reduction of nicotinamide adenine dinucleotide (NAD+) to NADH, with resulting increase in the ratio of NADH/NAD+, which supports a possible mechanism for the inhibition of hepatic gluconeogenesis (HGN) and corroborates the occurrence of alcohol-induced hypoglycemia, especially in malnourished individuals where renal and hepatic glycogen stores are compromised (Sumida et al., 2007). Retrospective studies of acute hypoglycemia in adults requiring hospital admission identified prevalence of alcohol induced - hypoglycemia to be between 7.01% - 17.64% patients (Bartlett, 2995; Lionte et al., 2004).

Aim of the study

Our objective is to assess the relevance of a 5-hours prolonged OGTT in evaluation of the glucose metabolism disturbances in patients with acute and chronic ethanol poisoning, as compared with standard methods, such as FBG and 2h-OGTT. Thus, this category of patients who address to a large group of medical specialties (internal medicine, endocrinology, gastroenterology, emergency medicine, family medicine, psychiatry) can be better managed.

Patients and methods

This cross-sectional study included 497 consecutive patients with acute and chronic ethanol poisoning, who were admitted in the Medical Clinic of "Sf.Ioan" Emergency Clinical Hospital Iasi between January 2006 untill October 2008 and agreed to enroll in this study. The study was in accordance with the ethical standards of the Helsinki Declaration (World Medical Association, 2000), and the institutional ethics committee approved it. The data are presented according with the 2008 update of requirements for manuscripts submitted to biomedical journals (ICMJE, 2008).

Methods

All patients diagnosed with acute or chronic ethanol poisoning, from which we obtained an informed consent (from the patient or from next-of-kin in the situation of comatose patient) were included in the study. Exclusion criteria were represented by: diagnosis of DM, present history of cancer, renal disease, and liver disease (other than ALD). We excluded patients presenting with hypoglycemia secondary to other etiology, as well as subjects treated with beta-blockers, salicylates, thiazides, or cholesterol lowering medications. The patients were divided into 3 groups: subjects with acute ethanol poisoning requiring hospital admission: group 1, patients with drunkenness requiring assistance only in the ED for up to 24 h – group 2, and patients with chronic ethanol poisoning admitted for a medical condition – group 3. On admission of each patient, in clinic or ED, a 20-ml blood sample was immediately drawn. Blood ethanol level (BEL), blood glucose level (BGL), liver function tests (alanine transaminase – ALT, aspartate transaminase – AST, alkaline phosphatase – ALP, total bilirubin – TBIL, direct bilirubin, gamma glutamyl transpeptidase – GGT, coagulation tests, lactate dehydrogenase – LDH, albumin, total protein and electrophoresis), and toxicological screen (barbiturates, benzodiazepines, phenothiazines, amphetamines, analgesics, antidepressants, narcotics and drug abuse screen) were determined by standard laboratory techniques. At the same time, information was recorded for each patient regarding age, sex, weight, mental state, level of consciousness, time since last consumption of food, and usual alcoholic beverage, assessed using CAGE questionnaire (Ewing, 1984). Evaluation of alcohol units' ingestion was performed. The next day after their admission we performed in all these patients the 75 g OGTT, in accordance with the WHO criteria, prolonged to 5- h (Alberti & Zimmet, 1998; Belfiore & Mogensen, 2000). The blood samples were obtained at baseline and every 60 minutes thereafter for 5 h. Before data analysis, a glucose concentration ≤ 70 mg/dL was defined as hypoglycemia (ADA, 2005). We classified the curves obtained after 5-h prolonged OGTT (Figure I.27) into five types, according with literature data.

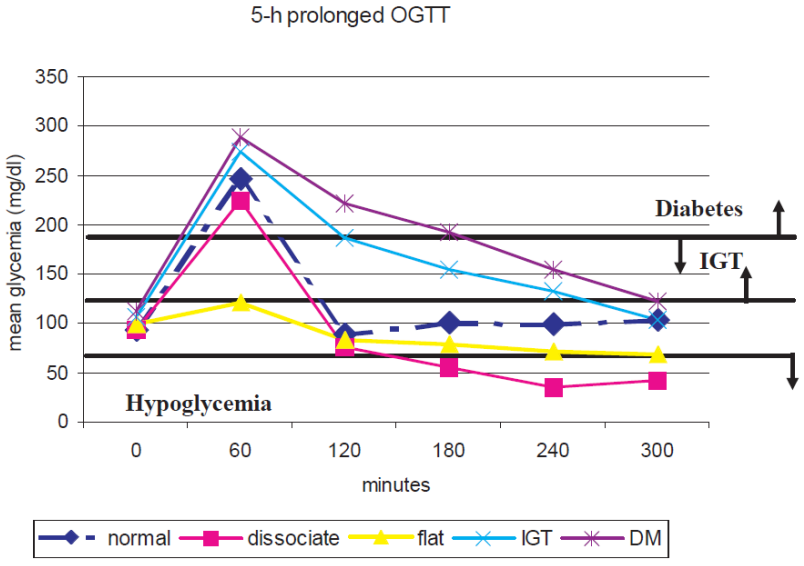


Figure I.27. Types of OGTT curves recorded in the study.

- Normal curve: fasting plasma glucose (FPG) < 100 mg/dL, 120 minutes post-glucose load < 140 mg/dL (ADA, 2006);

- Dissociate curve (with delayed hypoglycemia or hypoglycemic curve): FPG < 100 mg/dl, 60-minutes post-glucose load > 180 mg/dL, 120-, 180-, or 240-minutes post-glucose load < 50 mg/dL (Lionte, 2004);
- Flat curve: maximum plasma glucose after glucose load is below 120 mg/dL (Lionte, 2004);
- IGT curve: plasma glucose 120 minutes post-glucose load is 140 –199 mg/dL (ADA, 2006);
- Diabetic curve: plasma glucose 120 minutes post-glucose load is ≥ 200 mg/dL (ADA, 2006).

Abdominal ultrasonography and computer tomography were used to assess liver steatosis, and endoscopic examinations were performed during routine medical practices to evaluate the presence of esophageal varices and portal hypertensive gastropathy in patients with liver cirrhosis.

Statistical analysis

All continuous variables were expressed as mean ± standard deviation. Comparison of characteristics at baseline between groups was performed by Student's *t*-test (for mean values and percentages) or the Chi-square test (to compare frequencies). P-values less than 0.05 were considered statistically significant.

Results

Over a 34-month period, we analyzed a number of 497 consecutive subjects admitted in our clinic with acute and/or chronic ethanol poisoning. Three hundred and fourteen of these were men (63.17%) and 183 (36.83%) were women. They were divided into 3 groups (Table I.35).

Table I.35. Characteristics of the study groups.

Parameter	Group 1	Group 2	Group 3 (n)
Total patients (M/W)	167 (130/37)	182 (117/65)	148 (96/52)
BMI (kg/m^2)	30.5 ± 3.9	30.8 ± 3.5	31.6 ± 3.7
Markers for ALD (n / %)	57 / 34.13	49 / 26.92	148 / 100
Admission BGL (% - p)			
Normal	62 - 0.04*	48 - 0.006&	90
Hypoglycemia	12 - 0.02*	27	0 - 0.03&
Hyperglycemia	26	25 - NS&	10 - 0.05*
FBG (% - p)			
Normal	55.17 - 0.007*	80.17 - NS&	90
IFG	44.83	19.83 - 0.001#	10 - 0.0000*
5-h OGTT curve (% - p)			
Normal	31.73 - 0.0003*	48.9 - 0.0006&	3.37
Hypoglycemic	30.54 - 0.014*	26.37 - 0.029&	63.51
Flat	13.77	11.53 - NS*	10. 81 - NS&
IGT	13.77	7.14 - 0.003*	4.72 - 0,001&
Diabetic	10.19 - 0.007*	6.04 - 0.003&	17.56

M - men; W - women; n - number of patients; NS - p value statistically non-significant; * comparison between group 1 and 3; # comparison between group 1 and 2; & comparison between group 2 and 3.

Group 1 included 167 subjects (aged 37.46 ± 13.44 years) which had acute ethanol poisoning requiring hospital admission; group 2 consisted of 182 patients (aged 38.08 ± 12.77

years) who were assisted only in ED for drunkenness; group 3 included 148 patients (aged 47.67 ± 12.71 years) which had chronic alcoholism and were admitted for other various medical conditions.

Group 1 was composed of 77.84% men and 22.16% women. Forty-two patients (12.03%) with acute ethanol poisoning (groups 1 and 2) associated poisoning with another drug or toxin. Most of the drugs associated were CNS depressants, and the toxins (other than ethanol) involved were pesticides and caustics. Forty-nine acutely intoxicated patients (14.04%) had a history of psychiatric illness.

Glycemia upon admission, FBG and types of curves obtained after 5-h prolonged OGTT started at 7 a.m. the next day after admission were interpreted in accordance with criteria accepted today (Table I.36) and the results are presented in Table I.35.

Table I.36. Diagnostic values of glycemia (from ADA, 2005; ADA, 2006)

Category	Fasting plasma glucose (FPG)	OGTT
Normal	< 100 mg/dL (5.6 mmol/l)	2-h post load glucose < 140 mg/dl (7.8 mmol/L)
Hypoglycemia	≤ 70 mg/dL (3.9 mmol/l).	-
Impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)	100-125 mg/dL (5.6-6.9 mmol/L)	2-h post load glucose 140-199 mg/dL (7.8-11.1 mmol/L)
Diabetes (provisional diagnosis)	≥ 126 mg/dL (7.0 mmol/L)	2-h post load glucose ≥ 200 mg/dL (11.1 mmol/L)

Acute ethanol poisoning (according to literature classification) was mild in 18% patients, moderate in 22%, and severe (ethanol coma) in 60% cases from group 1 (Lionte, 2004). BEL was 0.5–1.5 g/L in 22.55% cases, 1.5–2.5 g/L in 25.36% cases, and over 2.5 g/L in 52.09% patients; BEL correlated well with severity of clinical form of ethanol poisoning. Group 2 was composed of 64.28% men and 35.72% women. Their comorbidities included: traumatic disorders – 47.17% cases, medical disorders – 52.73%. BEL was 0.5-1.5 g/L in 67.27% patients, and 1.5-2.5 g/L in 32.73% cases. All patients in this group had a mild/moderate form of ethanol poisoning. Glycemia upon arrival in ED, FBG and prolonged OGTT performed the next day are presented in Table I.35.

Group 3 consisted of 64.86% men, and 35.14% women. All these patients had ALD, as follows: hepatic steatosis 23%, chronic alcoholic hepatitis 45%, compensated liver cirrhosis 32% patients.

Ultrasound - measured hepatic left lobe volume in obese patients (BMI - 31.6 ± 3.7 kg/m2 in this group) was 433 ± 215 mL (range 46-1019 mL). Liver cytolysis was present in 67% patients (AST 101 ± 17 IU/L). Markers of chronic ethanol intake were present in all patients (GGT 135 ± 23 IU/L, MCV 102 ± 4.12), and all of them recognized a history of chronic drinking, confirmed by CAGE questionnaire. The results of BGL obtained on admission of group 3 (which in this group was in fact FBG), and results of 5-h OGTT are presented in Table 1. In this group hypoglycemia was elicited after prolonged OGTT.

Analysis of BGL showed that hyperglycemia in women of group 2 assisted in ED (50%) was significantly higher, compared with women in group 1 (18.18%, p 0.03), and group 3 (10.13% p 0.02). Men of group 1 had significantly more normal 5-h OGTT (34.29%) as compared with men of group 3 (0%, p 0.02). Age distribution analysis on group 1 showed a

higher percentage of normal BGL in patients aged between 30-60 (13.86%), compared with those below 30 (6.8%, p 0.03). Hypoglycemia was recorded more frequently in patients < 30 years old (5.82%), compared with those between 30-60 (1.81%, p 0.03). Into group 2, hypoglycemia was more frequent in patients aged 30-60 (14.46%), compared with patients < 30 years old (1.85%, p 0.007). In group 3, normal BGL was recorded significantly more in patients aged 30-60 (44.6%), and above 60 years old (45.4%), compared with those aged < 30 years old (0%, p 0.01). Analysis of patients in all three groups showed that normal 5h-OGTT appeared to be more frequent in patients aged 30-60 (40.74%) as compared with patients < 30 years old (15.38%, p 0.01), and those > 60 years old (7.69%, p 0.01). IGT was significantly higher in patients aged > 60 years old (21.74%) as compared with patients aged below 30 (2.04%, p 0.03).

The correlation of BEL with BGL (in groups 1 and 2) showed that when BEL is 0.5-1.5 g/L, hypoglycemia appeared more frequently (69.03%) as compared with normal glycemia (14.69%, p 0.0003) and hyperglycemia (16.28%, p 0.008), most of them being fasting alcoholic hypoglycemia. Relative time from last meal was 22 ± 2 hours in these patients. When BEL is 1.5 – 2.5 g/L, there were significantly increased abnormal values of glycemia: hyperglycemia (46.51%) significantly higher than normal BGL (10.99%, p 0.0005), and hypoglycemia (42.5%) significantly higher than normal BGL (10.99%, p 0.0001). Analysis of BEL correlated with types of OGTT curves showed that when BEL is higher than 2.5 g/L, there were more frequent IGT curves (50%) as compared with normal curves (18.18%, p 0.02), diabetic curves (11.1%, p 0.02), flat curves (15%, p 0.03), and dissociate curves (5.7%, p 0.005).

Analyzing glycemia in all three groups, in relation to chronic alcoholism, we find that hypoglycemia is more frequent in patients with chronic ethanol poisoning – 207 (79.92%), compared with normal BGL – 26 patients (10.04%, p 0.0001), and hyperglycemia – 26 patients (10%, p 0.0001). Dissociated curves (delayed hypoglycemia) in 5h-prolonged OGTT were significantly more frequent in chronic alcoholics – 105 patients (40.5%) as compared with normal curves – 59 patients (22.77%, p 0.04) – Figure I.28.

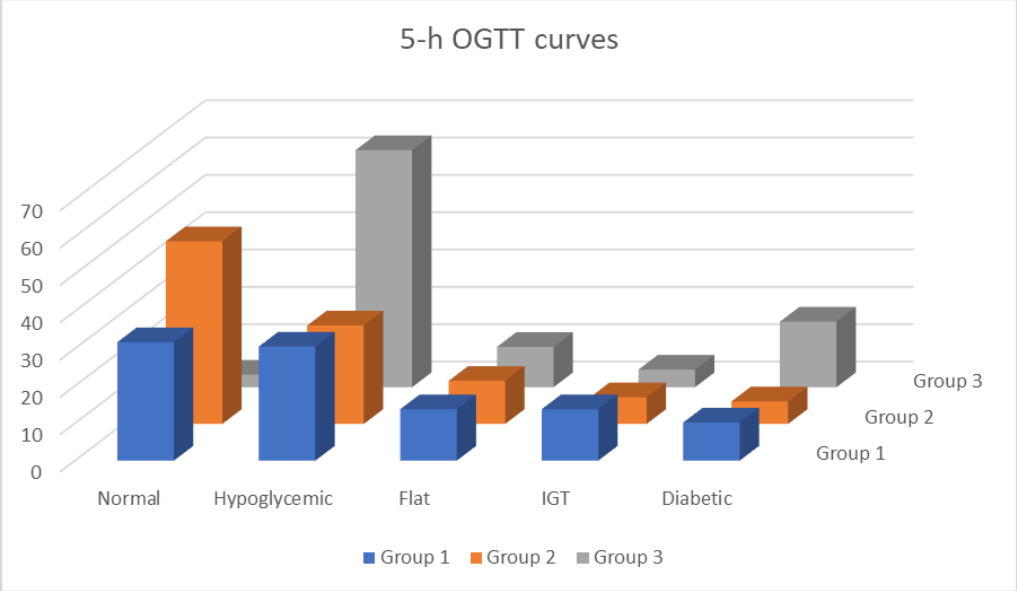


Figure I.28. Comparison of 5-h OGTT curves obtained in study groups.

All three groups included patients with obesity (BMI>30 kg/m2). Analysis of all 3 groups of patients showed that, based on 5 h prolonged-OGTT, DM was diagnosed in 54 subjects (10.86%), IGT in 43 subjects (8.65%), and delayed hypoglycemia in 172 subjects

(34.60%). 147 subjects (29.57%) had normal glucose tolerance. Glucose metabolism abnormalities were recorded in 143 subjects with chronic ethanol poisoning and ALD (96.63%), and in 207 cases with acute alcohol poisoning (59.31%), of which 106 (51.2%) had markers for ALD.

Discussion

In our study, patients with a mild form of acute ethanol poisoning had a significantly higher rate of hypoglycemia upon arrival, compared with normal blood glucose levels or hyperglycemia, because the majority of them had an elapsed time from last meal of 22 ± 2 hours, which probably determined a depletion of glycogen stores. Blood glucose homeostasis depends on several factors, especially exogenous intake, variations of its utilization, and in the situation of ethanol consumption (sometimes referred to as "alcohol"), on the effect of ethanol on gluconeogenesis (Lionte, 2004).

In a healthy-appearing patient, the first cause of a hypoglycemic disorder is ethanol (Service, 1995). Since the first description of alcohol induced-hypoglycemia (Brown & Harvey, 1941), frequent clinical reports document the association of alcohol ingestion with dysglycemia, both in nondiabetics and in patients with diabetes (Kolacinski & Rusiñski, 2003; Wilson & Waring, 2007; Jain et al., 2002; Lionte et al., 2004; Ngatchu et al, 2007; Kadono et al., 2007). In a fasted state, where both renal and hepatic glycogen stores are limited, the gluconeogenetic capacity within these organs is elevated, making it the primary mode to maintain blood glucose concentrations (Lionte, 2004). Once glycogen stores are depleted, hypoglycemia may develop because ethanol impairs gluconeogenesis.

Larger alcohol intake with longer than 24 hours duration of fasting are associated with a greater degree of hypoglycemia (Jain et al., 2002; Lionte et al., 2004). The mechanism of ethanol – induced alteration in blood glucose concentration is complex, but reasonably well understood (Lionte et al, 2004; Lionte et al., 2005; Kadono et al., 2007). If hepatic glycogen stores are adequate, the combination of alcohol-induced glycogenolysis and decreased glucose uptake into muscles result in an elevation in blood glucose concentration. For example, administration of 150 ml whisky to human subjects results in an increase of glycemia in 30-60 minutes. The concentration of blood glucose then decreases more rapidly than in control subjects not receiving alcohol (Freinkel & Arky, 1966; Lionte et al., 2005). A moderate dose of alcohol (0.5 g/kg body weight) significantly impaired glucose tolerance in normal subjects. Consumption of larger doses of alcohol (266 to 513 ml, consumed over 1 to 3 days) resulted in glucose intolerance in both normal and diabetic subjects (Patel, 1989). In our study, subjects acutely poisoned with ethanol had hyperglycemia recorded on admission in 90 of 349 patients (25.78%). In these patients (groups 1 and 2), types of OGTT curves recorded 24 h after admission (when BEL decreased in all patients < 0.01 g/L) demonstrate that hypoglycemia occurred in 26 – 31% subjects. Hypoglycemia can occur even after alcohol is no longer detectable in the blood if glycogen stores are not replenished (Jain et al., 2002). When we analysed BGL correlated with BEL, we find that at BEL 0.5-1.5 g/L, hypoglycemia appeared significantly more than normal BGL, or hyperglycemia in over two thirds of patients. Moderate ethanol consumption induces several metabolic changes in glucose, and lipid metabolism. These changes all take place without a significant effect of ethanol on beta-cell secretion. This implies that ethanol does not cause significant modification in beta-cell function. However, the presence of reduced plasma insulin concentration during experimental conditions would support the hypothesis that ethanol might increase insulin clearance (Lionte et al., 2006; Avogaro et al., 2002). The mechanism of reactive alcohol-induced hypoglycemia is secondary to hyperstimulation of insulin (twice normal values) when BEL is 0.5-1 g/L. Levels < 0.5 g/L have no effect, and levels > 1 g/L can even induce inhibition of insulin secretion (Lionte, 2004).

This biphasic effect of ethanol on blood glucose concentration reflects initial stimulation of glycogenolysis and subsequent impairment of gluconeogenesis from lactate by alcohol (Lionte & Hurjui, 2003; Lionte et al., 2005). It is well known that acute alcohol consumption inhibits HGN.

Chronic ethanol ingestion also determines a decrement in gluconeogenic capacity, which results in a greater susceptibility for alcohol-induced hypoglycemia, given the fact that some alcoholics tend to reduce their food intake and/or consume diets low in carbohydrates (Lionte, 2004; Sumida et al., 2007; Lionte et al., 2005). Our study finds prevalence of hypoglycemia to be significantly higher than normal BGL or hyperglycemia in chronic alcoholics. In adults, hypoglycemia typically occurs in chronic alcoholic patients with a history of poor dietary intake (Lieber, 2003). In chronic alcoholics, because of the NADH excess, gluconeogenesis from lactic acid and alanine is blocked, which could also explain their predisposition to hypoglycemia, especially when glycogen stores are depleted (Lionte, 2004). The majority of patients of group 3, with ALD and chronic ethanol poisoning, had abnormal OGTT curves. Flat curve represents the expression of a hyperinsulinism, which is frequent in the initial stages of diabetes mellitus (prediabetes, latent diabetes, or chemical diabetes), and in metabolic syndrome, being a physiological manifestation only in children. The abnormal curves recorded are the expression of carbohydrate metabolism disturbances encountered in ALD, as well as in other chronic liver diseases (Lionte et al., 2005; Lionte et al., 2006).

BMI was elevated in all 3 groups. In obesity, the secretome (adipokines, cytokines, free fatty acids and other lipid moieties) of fatty tissue is amplified, which through its autocrine, paracrine actions in fat tissue and systemic effects especially in the liver leads to an altered metabolic state with insulin resistance (IR). IR leads to hyperglycemia and reactive hyperinsulinemia, which stimulates lipid accumulating processes and impairs hepatic lipid metabolism. IR enhances free fatty acid delivery to liver from the adipose tissue storage due to uninhibited lipolysis. These changes result in hepatic abnormal fat accumulation, which may initiate the hepatic IR and further aggravate the altered metabolic state of whole body (Qureshi & Abrams, 2007). IR can explain the metabolic status of these cases and deserves attention. In addition, liver steatosis might impact glycogen production and glucose release. This could also contribute to the pattern of OGTT curves recorded, especially in group 3. Dissociate curves recorded in 5h-prolonged OGTT are elements that can be missed when OGTT is performed as recommended by WHO (fasting, 60 and 120-minute post load glucose determinations). They are particularly significant, because they are the expression of profound anomalies, as is the alteration of liver glucose production, secondary to collapse of glycogen stores and/or hepatic enzymes, expressed by this delayed hypoglycemia, 3-4 hours after glucose load. Both flat and dissociate curves on 5-h prolonged OGTT show a hyperinsulinism responsible for hypoglycemia, in the presence of an affected liver, feature which is relatively frequent, but ignored.

Alcohol itself has anti-insulin effects mediated by at least 2 mechanisms. The first mechanism is the direct aggression on beta-islet cells with appearance in time of chronic calcified pancreatitis and pancreatic amyloidosis. The second mechanism is represented by an increase in catecholamine concentration (which has a demonstrated hyperglycemic effect), secondary to adrenal medulla hypersecretion, synaptic norepinephrine reuptake inhibition, and catecholamine degradation inhibition (Lionte et al., 2006). These extremely complex biochemical anomalies explain the variety of glucose metabolism changes in ALD from hypoglycemia to impaired glucose tolerance and diabetes. In patients with ALD from our study, hypoglycemia outlined by 5 hours prolonged OGTT could be the expression either of insulin excess, failed to be metabolized by an altered liver, or of glycogen hepatic stores depletion and incapacity of gluconeogenesis to contribute to glucose homeostasis by utilization of non-

carbohydrate substrates, gluconeogenesis enzymes being affected by chronic alcohol intake. In advanced stages of ALD, with liver cirrhosis and liver failure, even in patients known to have diabetes, hypoglycemia can occur, being an expression of profound and irreversible hepatocellular damage (Lionte, 2004). Impaired glucose tolerance, diagnosed after OGTT in 5% patients with chronic ethanol poisoning suggests decreased insulin activity, mainly secondary to insulin secretion alteration as an effect of direct aggression of ethanol on beta islet cells. Ignoring this stage leads to failure of pancreatic function, and diabetes onset. A decline in HGN capacity from three carbon precursors as a result of chronic ethanol consumption could elevate the risk of alcohol-induced hypoglycemia, while an increase in HGN capacity (especially in patients with alcohol-induced liver cirrhosis) might lead to an earlier onset for glucose intolerance (Sumida et al., 2007).

It has been reported that excessive alcohol consumption increases the risk of type 2 diabetes (Wannamethee et al., 2003). Excessive ethanol consumption also causes hyperlipidemia, diabetes and hypertension, constituting alcohol-related syndrome. These morbid conditions are secondary to mechanisms that are apparently independent from obesity, and are peculiar to ethanol consumption, such as shifts in the redox-state, abnormalities of the sympathetic nervous system, changes of hormonal secretions such as the renin angiotensin-aldosterone system and cortisol production, damage to the pancreas (Yokoyama et al., 2007).

In our study, women with drunkenness had significantly more frequent bouts of hyperglycemia on arrival in ED, while men were not statistically different when we analyzed BGL. On the other hand, men had significantly more normal OGTT when they were acutely poisoned with ethanol. There are differences in the liver's response to both an acute and chronic consumption of ethanol in men versus women. There are sex differences in the location and quantity of hepatic ADH and in the first-pass metabolism of ethanol, the latter of which can give rise to higher BEL in women as compared to men despite an equivalent consumption of ethanol (Baraona et al., 2001; Sumida et al., 2007). Men tend to have a higher gastric ADH activity compared to women, who has a higher hepatic ADH activity (Baraona et al., 2001). Also, women demonstrate a higher BEL as compared to men, even when the alcohol ingestion per body weight is equivalent (Li et al., 2000). The fact that men have higher gastric ADH activities, as Lieber demonstrated in 2000, results in a greater first-pass metabolism of alcohol compared to women and substantiates the higher BEL observed in females (Lieber, 2000). Also, there are differences in counter-regulatory response to hypoglycemia in alcoholic men compared to alcoholic women, who are more vulnerable for ethanol-induced hypoglycemia (Sumida et al., 2007; Lieber, 2000).

Analysis on age distribution of 5h-prolonged OGTT curves showed that normal OGTT curves are lower in subjects > 60 years old as compared with patients < 60 years old. Also, IGT was significantly higher in patients > 60 years old as compared with younger subjects (< 30 years old). Studies involving nondiabetic individuals have shown that elderly nondiabetic subjects exhibit deterioration in glucose tolerance after ethanol administration compared with younger men. Orally ingested ethanol has direct effects on hepatic glucose production, which may exacerbate or attenuate the tendency to hypoglycemia. Fatty acids play a critical role in glucose homeostasis during ethanol ingestion (Van de Wiel, 2004). Alcohol-induced suppression of non-esterified fatty acids prevents the normal lipolytic response to catecholamines during hypoglycemia (Kerr et al., 2007).

Conclusion

In our series of 497 patients, acute and chronic ethanol poisoning is more frequent in middle-aged men as compared to women. Both blood glucose levels (BGL) on arrival, and prolonged OGTT curves were correlated with blood ethanol levels (BEL). Hypoglycemia was

recorded in more than two thirds of acutely poisoned patients, when alcohol level was 0.5-1.5 g/L. Impaired glucose tolerance (IGT) was recorded in half of patients with BEL > 2.5 g/L. We demonstrated abnormal OGTT response in chronic alcoholics, especially delayed hypoglycemia, and IGT, as an indicator of alcoholic liver disease (ALD). Although the majority of patients had normal FBG, using 5 h prolonged-OGTT, we were able to diagnose multiple abnormalities of glucose metabolism, from DM (10.86%) and IGT (8.65%), to delayed hypoglycemia (34.60%). We consider that glucose metabolism abnormalities outlined by 5 hours prolonged OGTT in our patients is an argument to use this test in all patients with acute or chronic ethanol poisoning, especially in those with ALD, in addition to standard methods.

I.4. Risk assessment based on statistical methods

This direction of research is reflected in the following published articles:

1. **Lionte, C,** Sorodoc, V, Jaba, E, Botezat, A. Development and validation of a risk-prediction nomogram for in-hospital mortality in adults poisoned with drugs and nonpharmaceutical agents - an observational study. *MEDICINE* (Baltimore) 2017; 96 (12): Article Number e6404. DOI 10.1097/MD.0000000000006404 **(IF 2.028)**
2. **Lionte, C;** Sorodoc, V; Tuchilus, C; Jaba, E. Likelihood Estimation of the Systemic Poison-Induced Morbidity in an Adult North Eastern Romanian Population. *Romanian Statistical Review* 2016; 4: 87-99. ISSN 1018-046X; eISSN 1844-7694. **Emerging Sources Citation Index (ESCI)**

Estimation of the likelihood for poison-induced morbidity in adults

Background

Acute poisoning with xenobiotics represents a life-threatening situation and a global public health problem. According to the World Health Organization, 370,000 people die of acute self-poisoning each year globally, and the mortality is higher in low- and middle-income countries in Europe than in any other region in the world (Mathers et al., 2004). Acute exposure to a systemic poison (which affects the entire body at various degrees, with major effects manifested in at least two organs or systems) represents an important segment of acute poisoning and medical emergencies (Lionte et al, 2016). Our previous experience showed that acute drug poisonings represent the majority of the total number of poisoned patients in our area, with a mortality rate of 0.3% (Sorodoc et al, 2011). After exposure to chemicals such as cholinesterase inhibitors, the mortality rate in our area is 3.8% (Gazzi et al, 2015).

The poison's effect on an organism is measured using vital function parameters and laboratory tests. Based on the severity of a poisoning, the patient may develop one or multiple complications reflecting the poison-related morbidity. The management of a poisoned patient uses laboratory tests and specific biomarkers to assess the morbidity. Thus far, some investigators have documented the use of laboratory tests (i.e., arterial lactate level, MB isoenzyme of creatine kinase – CKMB, and troponin) as prognostic indicators in order to identify high-risk patients in acetaminophen, carbon monoxide (CO) or paraquat poisoning (Shah et al, 2011; Kao et al, 2009; Liu X.W. et al, 2013). There is little knowledge about the role of routine laboratory tests as early predictors for a systemic poison-induced morbidity.

Aim of the study

Our aim was to identify the factors influencing the in-hospital morbidity of a cohort of patients acutely exposed to systemic poisons, and to determine the value of conventional

laboratory tests obtained upon admission, combined with different demographic and clinical characteristics, for likelihood assessment of the subsequent morbidity in a tertiary referral center from North East Romania. The physician could immediately use these clinical and laboratory data to identify patients at risk for developing complications or death and improve their management, early referring these patients to an intensive care unit (ICU).

Methodology

Study Design and Setting

This work was designed as a prospective observational study in a tertiary referral center for toxicology, admitting patients from North East Romania with acute poisoning. Over a period of 15 months (April 1st 2015 – 31st March 2016), we enrolled consecutive patients with a diagnosis of acute poisoning, which were admitted in the Medical Clinic, or in the ICU of the "Sf. Spiridon" Emergency County Clinic Hospital, Iasi. All subjects or their families (in the situation of an unconscious patient) signed an informed consent prior to the enrollment. The study was funded by an internal research grant of the university, and approved by the Ethics Committee.

Selection of Participants

The study included hospitalized patients acutely exposed to a systemic poison, older than 18, irrespective of gender. Patients were poisoned with prescription drugs, illicit drugs, miscellaneous chemicals (pesticides, toxic alcohols, hydrocarbons etc.), toxic gases or were exposed to multiple systemic poisons. Patients without a signed informed consent, younger than 18 years, with a history of diabetes, with exposure to a poison with a local irritant effect, or with an acute pathology associated to poisoning (i.e., trauma, burns, etc.) were excluded from our study.

Patient assessment

All patients with a confirmed diagnosis of acute intoxication with a systemic poison, based on clinical examination, and toxicological tests, underwent routine assessment (complete blood count, arterial blood gases, glucose, electrolytes, C reactive protein, troponin I, BNP, creatine phosphokinase - CK, CKMB, myoglobin, renal and liver function profile). Patients were clinically monitored, by means of electrocardiogram (ECG), pulse oximetry and non-invasive blood pressure measurements. The management of these patients involved measures of basic life support, special interventions in case of respiratory failure, shock, and cardiac arrest, decontamination measures, supportive and antidote therapy, which were continued after admission in the medical clinic, or ICU, as recommended by the guidelines.

The main objective was to assess the poison-related morbidity during hospitalization. Patients were divided into three groups: without morbidity (no complications during hospitalization), with a mild morbidity (only one complication involving a single organ or system resolved during hospital stay), and with severe morbidity (defined as in-hospital multiple complications and/or death). The presence of an early complication was defined as follows: central nervous system complication (coma, stroke, or seizures); rhabdomyolysis (CK > 1000 IU/L); acute respiratory failure, defined as a condition requiring mechanical ventilation for correction of hypoxia, or hypercapnia, for more than 24 hours; cardiovascular complications (hypotension, defined as systolic blood pressure less than 90 mm Hg, or arrhythmias with circulatory compromise, and acute myocardial injury, based on cardiac biomarkers and ECG); acute liver injury, defined as markedly elevated serum alanine and aspartate aminotransferase levels > 10 times the upper limit of the normal range, accompanied

by mild or moderate elevations in alkaline phosphatase levels (Chalasani et al, 2014); acute kidney injury, defined as urine volume <0.5 ml/kg/h for 6 hours, based on KDIGO criteria (Kidney inter., Suppl, 2012); gastro-enteral, defined as lesions indicated by a superior or inferior digestive endoscopy; multiple complications (at least two organs or systems affected).

Statistical analysis

Numerical variables are presented as mean ± SD, median with interquartile range, or frequency for categorical variables. To identify significant differences between the patient morbidity groups defined, taking into account clinical and demographic data, laboratory tests associated with poisoning-related complications and fatalities, Student's t test or Mann-Whitney U test for normal distributed variables, as well as the Chi-square test and Cochrane's statistic for categorical variables were used to perform univariate analysis (Jaba and Grama, 2004). We calculated p (Sig.) for the differences between parameters for patients with or without morbidity. A Sig. < .05 was considered statistically significant. All variables found to be significant in the univariate analyses for morbidity were subjected to a logistic regression analysis. First, we applied simple binomial logistic regression for each statistically significant variable. Then we applied multinomial logistic regression on variables characterizing different systems and organs. Risk was expressed as odds-ratios (OR) with confidence intervals (CI). Goodness-of fit for multivariate models was confirmed using Hosmer and Lemeshow test. The receiver operating characteristic curve (ROC) was used as a measure of diagnostic performance, to validate the discriminatory power of the model predictive variables (Hajian-Tilaki, 2013). Statistical analyses were performed with SPSS (version 22.0; SPSS, Inc., Chicago, IL).

Results

During the study period, 180 patients were enrolled with a mean age of 44.7 ± 17.2 years (range, 18-90 years), 51.1% males, all Caucasians. The majority of cases were self-poisonings (91.1%), 16 cases being accidental poison exposures. The mean time interval between poison exposure and admission was 5.5 ± 1.9 hours. The population's demographic, clinical, and laboratory characteristics based on the morbidity recorded are presented in the Table I.37. Poisoning with prescription drugs (37.22%), followed by the combination of poisons (29.44%) represented the majority of agents used in self-poisoning by our patients (Figure I.29).

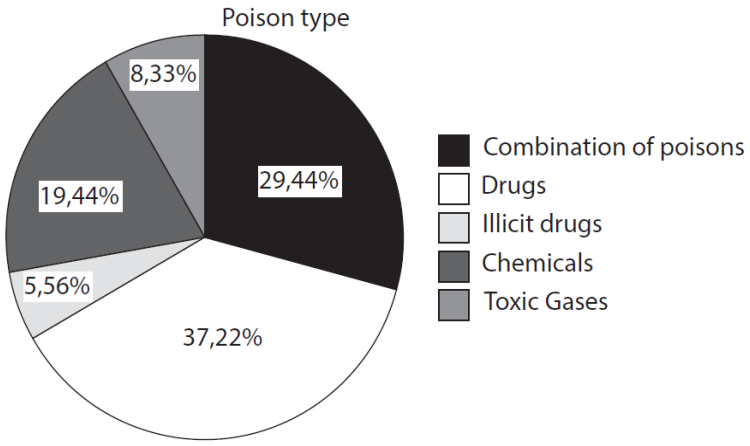


Figure I.29. The poisons involved in acute poisoning of the cohort analyzed.

Table I.37. Characteristics of the observed variable distribution in total cohort and groups of patients

Variable	Total N=180 patients	No complication N=89 patients	Single complication N=52 patients	Multiple complications N=39 patients	Sig.
Demographic data					
Age (years)	44.7 ± 17.2	42.3 ± 15.7	42.1 ± 17.4	53.4 ± 17.6	.001
Gender; F/M (%)	88/92 (48.9/51.1) *	54/35 (61.4/38)	20/32 (22.7/34.8)	14/25 (15.9/27.2)	.007
Origin; R/U (%)	90/90 (50.0/50.0) *	51/38 (56.7/42.2)	23/29 (25.6/32.2)	16/23 (17.8/25.6)	.146
Clinical and toxicological data					
GCS; N (%)					
> 8	146 (81.1) *	86 (58.9)	42 (28.8)	18 (12.3)	.000
≤ 8	34 (18.9) *	3 (8.8)	10 (29.4)	21 (61.8)	
HR (beats/min)	91.63 ± 24.47	86.91 ± 18.73	92.81 ± 25.44	100.85 ± 31.61	.011
SBP (mmHg)	123.59 ± 25.40	122.15 ± 21.31	125.54 ± 24.28	124.31 ± 34.44	.734
DBP (mmHg)	75.65 ± 14.71	76.36 ± 12.64	76.71 ± 14.17	72.62 ± 19.19	.346
Poison involved; N (%)					.001
Combinations	53 (29.4) *	31 (58.5)	14 (26.4)	8 (15.1)	
Prescription medicines	67 (37.2) *	41 (61.2)	13 (19.4)	13 (19.4)	
Drugs of abuse	10 (5.6) *	4 (40.0)	6 (60.0)	0 (0.0)	
Chemicals	35 (19.4) *	10 (28.6)	11 (31.4)	14 (40.0)	
Toxic gases	15 (8.3) *	3 (20.0)	8 (53.3)	4 (26.7)	
Laboratory tests					
Lactate (mmol/L)	3.08 ± 3.16	2.49±2.53	2.84±2.31	4.74±4.61	.001
pH	7.36 ± .13	7.41 ± .06	7.37± .09	7.22± .21	.000
Base excess (mmol/L)	22.86±5.17	24.68±2.89	23.39 ± 4.09	17.99 ± 7.19	.000
Sodium (mEq/L)	140.37±5.71	140.29±3.53	141.88±5.35	138.51±8.93	.019
CRP (mg/dl)	1.82±4.59	.63 ± 1.33	1.66 ± 4.84	4.76 ± 7.17	.000
WBC (*1000/mcgL)	10.43 ± 4.88	8.16 ± 2.53	11.09 ± 4.61	14.74 ± 6.10	.000
Hemoglobin (g/dL)	13.78 ± 1.61	13.51 ± 1.56	14.08 ± 1.21	13.98 ± 2.07	.084
Glycemia (mg/dl)	131.05 ± 55.34	115.79±36.92	124.40±32.48	174.74±85.37	.000
Creatinine (mg/dl)	.89 ± .42	.80 ± .22	.81 ± .20	1.18 ± .74	.000
ASAT (U/L)	43.34 ± 78.63	23.22±12.14	41.23±57.24	92.08±144.89	.000
ALAT (U/L)	30.47±34.52	21.35±12.62	33.42 ± 38.64	47.33 ± 52.35	.000
Myoglobin (ng/mL)	109.45 ±151.62	49.29±27.63	96.67±100.33	263.78±244.69	.000
BNP (pg/mL)	77.28 ± 145.16	39.63±109.39	74.55±128.06	166.84±194.89	.000
CK (U/L)	646.76±4240.30	130.84±89.32	303.85±564.16	2281.31±8984.64	.023
CKMB (ng/mL)	8.12±12.87	5.08±7.78	8.05±10.86	15.14±20.24	.000
Management					
ICU therapy; N (%)					.000
Not needed	140 (77.8) *	85 (60.7)	41 (29.3)	14 (10.0)	
Administered	40 (22.2) *	4 (10.0)	11 (27.5)	25 (62.5)	
Antidote therapy; N (%)					.000
Nonexistent	95 (52.8) *	47 (49.5)	26 (27.4)	22 (23.2)	
Unavailable	2 (1.1) *	1 (50.0)	0 (0.0)	1 (50.0)	
Not indicated	46 (25.6) *	34 (73.9)	10 (21.7)	2 (4.3)	
Administered	37 (20.6) *	7 (18.9)	16 (43.2)	14 (37.8)	
Hospitalization (days)	4.5 ±3.6	3.2 ±1.7	4.3 ±2.4	7.7 ± 5.8	.000

F, female; M, male; *, % of total; R, rural; U, urban; GCS, Glasgow Coma Scale score; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C reactive protein; WBC, white blood cells; ASAT, Aspartate Aminotransferase; ALAT, Alanine Aminotransferase; BNP, brain natriuretic peptide; CK, creatine kinase; CKMB, MB isoenzyme of creatine kinase; ICU, Intensive Care Unit.

Based on the significant differences between means, or frequencies of the considered patients' groups (no complications, a single complication or multiple complications) we

identified variables, which were included in the logistic regression analysis. Significant predictors of poison-related morbidity are shown in Table I.38.

Although patients with multiple complications were significantly older than patients without complications (Table I.37), old age (> 65 years) was not correlated with morbidity after logistic regression analysis, in acute intoxication with systemic poisons (Table I.38). Among the cardiovascular parameters, only the heart rate was significantly correlated with complications (Table I.37) but was not predictive for morbidity in our patients, after logistic regression analysis.

Table I.38. Variables influencing the morbidity identified using the simple binomial logistic regression.

	B	S.E.	Wald	Sig.	Exp (B)	95% C.I. for EXP (B)	
						Lower	Upper
CRP	.090	.091	.972	.324	1.094	.915	1.307
Base excess	.017	.070	.060	.807	1.017	.887	1.166
WBC	.240	.073	10.786	.001	1.272	1.102	1.468
Glycemia	.006	.005	1.113	.292	1.006	.995	1.017
Creatinine	-.282	1.032	.075	.785	.754	.100	5.700
ALAT	.035	.013	7.739	.005	1.036	1.010	1.062
Myoglobin	.017	.006	7.522	.006	1.017	1.005	1.029
BNP	.003	.002	2.384	.123	1.003	.999	1.006
CKMB	.039	.024	2.664	.103	1.040	.992	1.089
GCS ≤ 8	-2.625	.814	10.388	.001	.072	.015	.358
Age > 65 years	-.427	.746	.328	.567	.653	.151	2.814
Constant	-3.172	2.568	1.526	.217	.042		

CRP, C reactive protein; WBC, white blood cells; ALAT, Alanine Aminotransferase; BNP, brain natriuretic peptide; CKMB, MB isoenzyme of creatine kinase; GCS, Glasgow Coma Scale score.

On multivariable analysis, 4 of the 19 candidate variables were predictive of a single complication, and respectively 6 variables were predictive for multiple complications or death (Table I.39).

Table I.39. The significant variables influencing the morbidity identified after multinomial logistic regression.

Morbidity[a]		B	Std. Error	Wald	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower Bound	Upper Bound
Single complication	WBC	.232	.076	9.215	.002	1.261	1.086	1.465
	ALAT	.034	.014	6.381	.012	1.035	1.008	1.063
	Myoglobin	.013	.006	5.323	.021	1.013	1.002	1.025
	Prescription drugs	-1.779	.892	3.979	.046	.169	.029	.969
	GCS > 8	-2.325	.867	7.187	.007	.098	.018	.535
Multiple complications	WBC	.289	.101	8.223	.004	1.335	1.096	1.626
	Glycemia	.022	.008	7.504	.006	1.022	1.006	1.039
	ALAT	.055	.016	11.331	.001	1.057	1.023	1.091
	Myoglobin	.022	.007	11.727	.001	1.023	1.010	1.036
	BNP	.006	.003	5.102	.024	1.006	1.001	1.011
	Drugs of abuse	-19.246	.000	.	.	4.381E-9	4.381E-9	4.381E-9
	GCS >8	-4.718	1.171	16.240	.000	.009	.001	.089

[a] The reference category is: No complications. WBC, white blood cells; ALAT, Alanine Aminotransferase; GCS, Glasgow Coma Scale score; BNP, brain natriuretic peptide.

Upon admission to hospital, the patient characteristics that were most strongly predictive of in-hospital severe morbidity included high WBC count (33.5%), high ALAT level (5.7%), an increased myoglobin and glucose level, whereas a GCS > 8 was associated with a 9.8% reduction in mild morbidity, and 0.9% reduction of severe morbidity. Interestingly, an exposure to a prescription drug was associated with an 83.1% reduction in occurrence of a single complication (Table I.39). Of particular interest was the finding that acute exposure to drugs of abuse was associated with a lower risk of severe morbidity, such as multiple complications or death, particularly because in our region, the illicit drugs are used on a limited extent, while the substances associated with a major morbidity (such as cocaine) are expensive and not readily available. We checked the validity of our model using ROC methodology (Figure I.30).

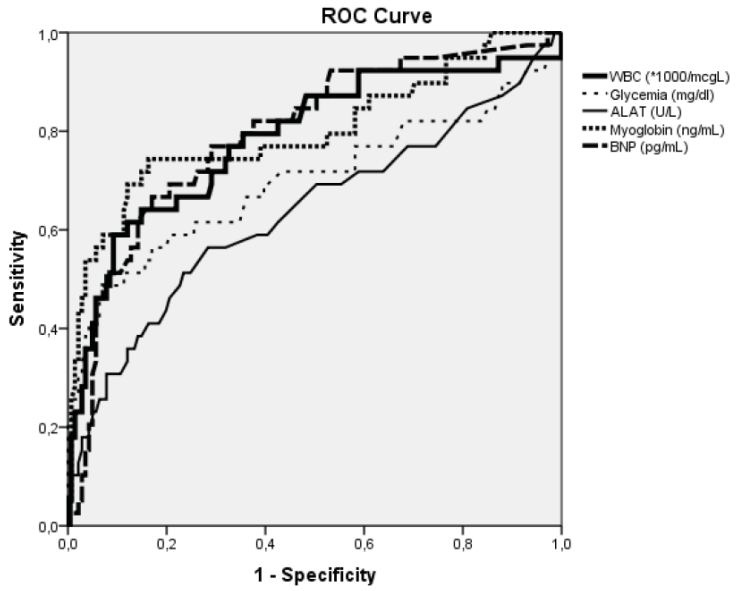


Figure I.30. Validation of the predictive variables for systemic poison-related morbidity with receiver operating characteristic curves.

Five of the observed variables showed a good discriminatory capacity, with an area under the ROC curve (AUC) > 0.5, as follows: WBC (AUC, 0.79; CI 95%, 0.69–0.88; p < .001), glycemia (AUC, 0.70; CI 95%, 0.58–0.81; p < .001), ALAT (AUC, 0.64; CI 95%, 0.53–0.75; p .01), myoglobin (AUC, 0.80; CI 95%, 0.71–0.89; p < .001), and BNP (AUC, 0.79; CI 95%, 0.71–0.88; p < .001). The optimal cut-off values, as resulted from this ROC analysis are: WBC 10.56 *1000/mcgL, with a 72% sensitivity and a 71% specificity, glycemia 115 mg/dL, with a 72% sensitivity and a 57% specificity, ALAT 57 U/L, with a 21% sensitivity and a 96% specificity, myoglobin 114 ng/mL, with a 69% sensitivity and an 88% specificity, and BNP 108 pg/mL, with a 49% sensitivity and a 92% specificity.

Complications recorded during hospitalization (Figure I.31) occurred in 91 patients (50.6%). Among those, 39 were patients with multiple complications (21.7%), and 17 were patients with cardiovascular complications (9.4%). Out of the 180 patients included, 16 patients died during hospitalization (8.9%) as a cause of multi-organ failure, having a length of hospital stay of 6.9 ± 5.9 days, significantly longer compared with the survivors (4.3 ± 3.4 days, p 0.005).

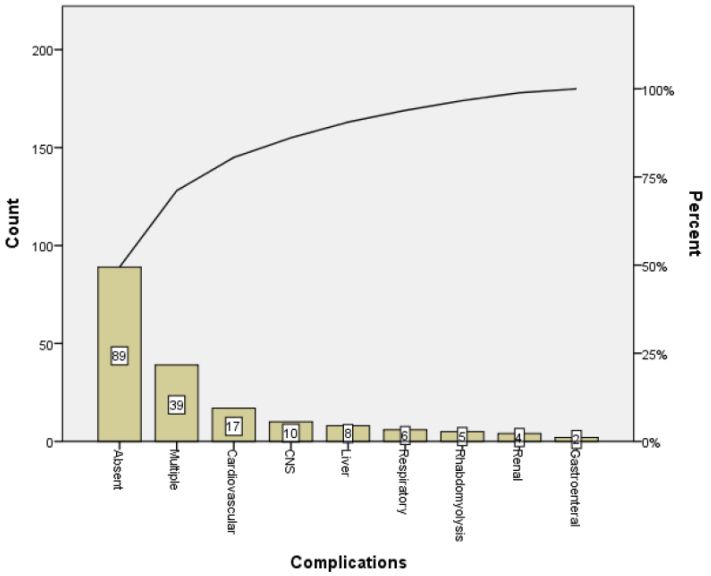


Figure I.31. Complications recorded in the cohort analyzed.

Discussion

Acute poisonings represent a worldwide problem. In our area, epidemiological data suggested that 97.27% are acute drug poisoning in suicide attempts, using combinations of drugs in 32.92% cases (Sorodoc et al, 2011). The reports from the National Poison Data Systems in United States show that poisoning with pharmaceutical products is the leading cause of accidental death (Dart et al, 2015), data that are consistent with epidemiological reports from Central Europe (Krakowiak et al, 2011). Poisoning with nonpharmaceutical agents, such as toxic alcohols, gases, and miscellaneous chemicals are associated with the largest number of fatalities, CO being the leading cause of death in the United States (Mowry et al, 2013).

Several retrospective studies attempted to identify prognostic or mortality indicators in acute poisonings, such as CO poisoning (i.e., lactate, cardiac biomarkers – Cervellin et al, 2014; Liu et al, 2014), or pesticide poisoning (acid-base status, male sex, or age), (Liu et al, 2008; Hsu et al, 2013). It was argued before, after a retrospective analysis, that some indicators, such as toxicological history, Glasgow Coma Scale (GCS) score, or serum lactate level, could help the emergency physicians to distinguish between low and high-acuity poisoned patients with deliberate drug poisoning, in order to avoid excessive morbidity (Maignan et al, 2014). Our previous experience showed that there are some indices available upon the arrival of a patient acutely exposed to a systemic poison, such as the poisoning severity score, a GCS < 10, initial and 4h-arterial lactate level, brain natriuretic peptide (BNP), and 6h-CKMB, which can early predict a poor short-term outcome, and mortality (Lionte et al, 2016).

The logistic regression models have been extensively used during the last years in medical research, including toxicology (Hunt and Li, 2006), dentistry (Javali and Pandit, 2012), or epidemiology (Bender, 2009), etc. Multivariable statistical models can be useful tools for the prognosis prediction, when are developed accurately (Harrell et al, 1996). The goal of an analysis using a logistic regression model is to find the relationship between response variable and a set of factors. In order to have an accurate model, a reduced number of variables, or a simplified model must be used (Harrell et al, 1996). To investigate the risk factors associated with poison related morbidity, outcomes or mortality, the regression methods have become an important component of any data analysis regarding to the relationship between a response variable (i.e., outcome or death) and one or more predictor variables called factors (i.e., age,

poisoning severity score, etc). Receiver operating characteristic (ROC) curve analysis was used extensively for the assessment of diagnostic ability of laboratory tests and for the classification of diseased from the healthy subjects using imaging tests in the last several years (Hajian-Tilaki, 2013).

Some limitations in this study should be mentioned. There could be a possible selection bias in the population studied, which included patients from a single tertiary center in North East Romania, although the epidemiological and toxicological data are consistent with those reported in other areas. (Dart et al, 2015; Krakowiak et al, 2011) We could not calibrate the influence of toxin serum concentration (because the quantitative toxicological tests are not available immediately after admission in the majority of poisoning). We failed to monitor the morbidity of the patients exposed to a systemic poison after discharge from the hospital.

Conclusions

Early prediction of clinical decompensation and subsequently morbidity in patients acutely exposed to a systemic poison is limited. The main objective of our study was to identify and analyze the determinants of the morbidity in a cohort of patients with acute systemic poisoning, and to estimate the value of conventional laboratory tests obtained upon admission, combined with different demographic and clinical characteristics, to assess the likelihood of in-hospital morbidity. To the best of our knowledge, this is the largest cohort of patients exposed to systemic poisons prospectively analyzed in a Romanian tertiary center.

In order to identify the factors that mostly impact the poison-related morbidity, multiple logistic regression analysis was applied taking into account significant variables associated with the occurrence of complications, and the discriminatory power of the model predictive variables was validated using ROC analysis.

Our results suggest that the in-hospital morbidity for poisoned patients can be reliably identified with clinical parameters, such as the Glasgow Coma Scale score and routine laboratory tests obtained upon admission. Admission level of WBC, ALAT, myoglobin, glycemia and BNP are strong independent predictors of in-hospital severe morbidity.

The use of these parameters identifies poisoned patients, after exposure to a systemic toxin, at high risk for in-hospital severe morbidity, and who might benefit from careful monitoring and aggressive intervention. There is a need for further efforts to define the factors influencing morbidity and mortality risk for all patients hospitalized with acute poisoning.

A risk prediction nomogram for in-hospital mortality in poisoned patients

Background

Acute poisoning is potentially life-threatening and is an important medical emergency. Nomograms are widely used in different clinical settings, to indicate the probability of an event, such as death or disease recurrence, primarily by reducing statistical predictive models to a single numerical estimate tailored to the individual patient profile (Kuo et al., 2013). For example, in oncology, nomograms can help determine cancer prognosis (Iasonos et al., 2008) and offer an accurate individualized prediction of survival (Zhou et al., 2015), and in neonatology nomograms are used to assess the risk for severe non-physiologic hyperbilirubinemia after neonates' discharge (Romagnoli et al., 2012). They reduce statistical predictive models into a single numerical estimate, tailored to the profile of an individual patient, indicating the probability of an event, such as death or recurrence (Kuo et al., 2013).

In clinical toxicology, several nomograms have been developed, including the Done nomogram, indicating the severity of toxicity based on 6-hour levels of non-enteric-coated aspirin (Dugandzic et al., 1989), currently with limited clinical use; the Rumack–Matthew

nomogram, for antidote therapy decision in acetaminophen overdose (Rumack, 2002); the QT nomogram, predictive for arrhythmogenic risk of drug-induced QT prolongation (Chan et al., 2007), particularly in antipsychotic (Berling & Isbister, 2015), and antidepressant overdoses (Waring et al., 2010); and graphical nomograms predicting drug concentration (Pospisil & Pelclová, 1994). To be relevant for clinical practice, the accuracy of a risk assessment tool should be greater than that of a practitioner's assessment in the ED (Stiell & Wells, 1999).

Aim of the study

Our aim was to construct and validate a simple, accurate, and widely applicable nomogram offering an early estimate of the risk of in-hospital mortality, using objective data, immediately available upon presentation to the ED, derived from a population of subjects following acute poisoning with drugs and nonpharmaceutical agents, irrespective of the dose, route of exposure, or mechanism of toxicity. The emergency physician could use this simple tool to identify patients with acute poisoning at risk of death immediately after presentation, and optimize patient management by referring patients to an ICU, to prevent mortality.

Materials and methods

Study design

This paper presents the results of a prospective cohort study involving patients with acute poisoning, conducted in a tertiary referral center for toxicology (Figure I.32). Enrollment occurred between January 2015 and December 2015 (derivation cohort) and between January 2016 and June 2016 (validation cohort). The study was funded by an internal research grant awarded by the "Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania. This study complied with the principles of the Declaration of Helsinki and was approved by the "Grigore T. Popa" University of Medicine and Pharmacy's Commission for Research Ethics, and by the "Sf. Spiridon" Clinical County Emergency Hospital's Ethics Committee. The study complied with the transparent reporting of an observational cohort study (STROBE) and with a multivariable prediction model for individual prognosis (TRIPOD) statement (Collins et al., 2015).

Study setting and population

The setting for this study was an urban tertiary center with over 85,000 ED visits annually. Patients eligible for enrollment were over 18 years of age, with acute poisoning as the primary reason for hospital admission, and with admission occurring within 12 hours of exposure to a drug or chemical substance. We enrolled consecutive patients hospitalized in the ICU, or in a non-ICU ward, after obtaining a signed informed consent from the patient or the family (in the case of an unconscious patient). The following were exclusion criteria: lack of a signed informed consent, age under 18 years, diagnosis of diabetes, concomitant acute pathology associated with poisoning (such as trauma and burns, including chemical burns), or incomplete data.

Study protocol

Procedures were identical in the derivation and validation phases of the study. The following data were collected from all patients participating in the study: baseline characteristics, vital signs, mental status, underlying diseases, the type of poison exposure, the intent of the poisoning (self-harm or accident), coingestion of ethanol, laboratory test results, ECG and emergency echocardiography parameters, medical complications, antidote treatment patterns, ICU admission days, and in-hospital outcome. The patients were only followed up

during their hospitalization. The derivation cohort for nomogram development consisted of the 180 patients admitted between January 2015 and December 2015, with complete recordings of the parameters set out above. A standardized data collection form was designed to retrieve all the relevant information on socio-demographic data (age, sex, residence, ethanol exposure, history of chronic disease), baseline laboratory data, and biomarkers. Clinical scores, such as the Glasgow Coma Scale (GCS) and the Poisoning Severity Score (PSS), were recorded for all patients. In a subset of 20 patients (11.1%), blinded, independent second raters duplicated data collection to assess reliability (Stiell & Wells, 1999).

A blood sample was collected immediately after ED presentation to evaluate arterial blood gases, routine hematology and biochemical analysis, and cardiac biomarkers assessing myocardial injury (Thygesen et al., 2012). The results were obtained using ABL 90 (Radiometer, Denmark), PATHFAST Cardiac Biomarker Analyser (LSI Medience Corporation, Tokyo, Japan), Sysmex XT-4000i—Automated Hematology Analyzer (Sysmex Corporation, Tokyo, Japan), and ARCHITECT c16000 clinical chemistry analyzer (Abbott Laboratories, Abbott Park, Illinois, USA). A 12-lead ECG (to determine ST-T changes, PR, and QTc intervals) was recorded in the ED upon presentation. The QTc was calculated using the Bazett formula, and was considered prolonged if greater than 0.44 seconds (Chan et al., 2007). A transthoracic echocardiography using Fukuda Denshi Full Digital Ultrasound System UF-850XTD (Fukuda Denshi Co, Ltd, Tokyo, Japan) was performed in the ED by a cardiologist and an internal medicine specialist with competence in basic echocardiography, to assess systolic and diastolic function of the left ventricle (LV), as well as volume status, according to guideline recommendations (Lancellotti et al., 2015). The results were compared, the intra- and inter-reader variability was tested, and no statistical differences between the operators were noted.

Validation cohort

To examine the generalizability of the model, an external validation was performed using a separate cohort of 203 consecutive patients with acute poisoning after exposure to drugs or nonpharmaceutical agents, hospitalized in the same institution between January 2016 and June 2016, and 135 patients with complete data to score all the variables in the established nomogram were analyzed. No data from the validation cohort were used to derive the nomogram, and no data from the derivation cohort were used to validate it.

Key outcome measures

Patient status upon hospital discharge was defined as follows: survivors, defined as patients who survived and were discharged with stable vital signs, with no specific complaints, and with all complications resolved during hospitalization; nonsurvivors, defined as patients who died during hospitalization.

Data analysis

Each variable distribution was presented as mean ± SD, or median with interquartile range, or frequency. The Student' t test or Mann–Whitney U test for numerical variables, as well as the $\chi 2$ test and Cochrane statistic for categorical variables, were used to detect significant differences between survivors and nonsurvivors. To evaluate the association between patient data and mortality, we first applied simple binary logistic regression for each variable with significant differences between the 2 groups. Then we applied binary logistic regression on clusters of variables characteristic for systems and organs. We selected significant variables from each cluster, which were included in the final model. Odds ratios (OR) with confidence intervals (CI) were calculated. Goodness-of-fit for multivariate models

was confirmed using the Hosmer and Lemeshow test. Based on these results, we generated the nomogram. The receiver operating characteristic (ROC) methodology was used to assess the discriminative power of the nomogram. ROC analyses were expressed as curve plots and calculated area under the curve (AUC) with 95% CI and the associated P value representing the likelihood of the null hypothesis (AUC=0.5). Statistical analyses were performed using SPSS (version 22.0; SPSS Inc, Chicago, IL). We used STATA/SE 13.0, and the nomolog program to generate a Kattan-style nomogram, which is a nomogram for binary logistic regression predictive models (Zlotnik & Abraira, 2015). The length of the line corresponding to a given variable correlated positively with the importance of the variable (Zlotnik & Abraira, 2015). Internal validation was performed using the bootstrap method. The probability derived from the nomogram for all subjects was verified and compared with the value of the probability estimated using the logistic model. During external validation of the nomogram, the death risk probability for each patient was calculated using the established nomogram and logistic regression was performed using the predictive variables derived from the validation cohort. These probabilities were subjected to ROC analyses. In addition to comparing the discrimination ability of the AUC, we also calculated the positive predictive value (PPV) and the negative predictive value (NPV) of the scores calculated by the nomogram for the validation cohort. A 2-sided P value < 0.05 was deemed significant.

Results

Patient characteristics and survival

Among the 388 eligible patients (Figure I.32), 180 were included in the derivation cohort, and 135 patients were included in the validation cohort.

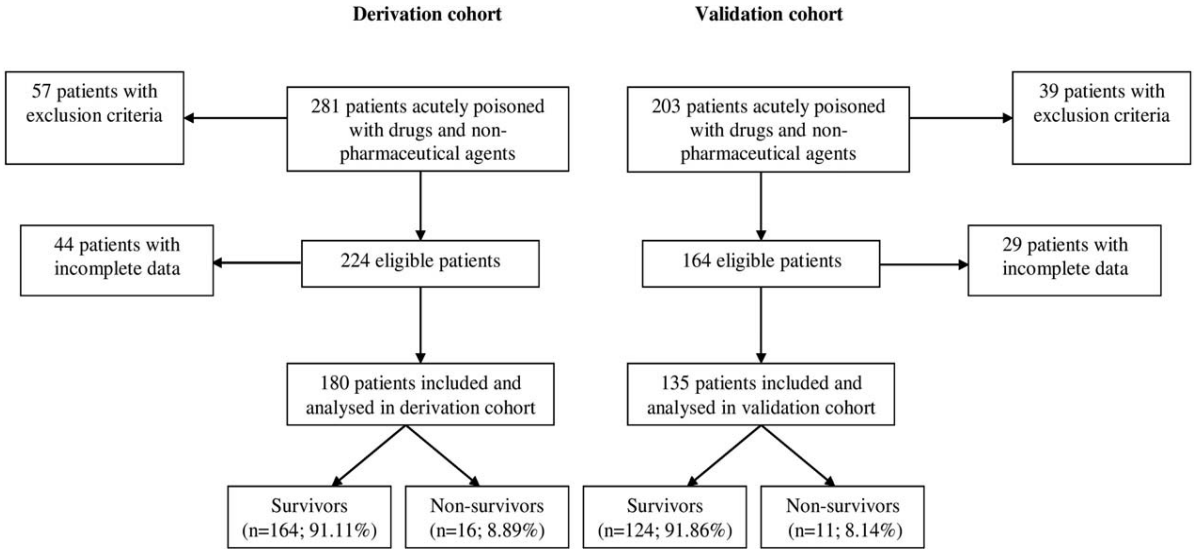


Figure I.32. Patient flow diagram.

We excluded 73 patients with incomplete data from the analysis. The patient's demographics, clinical characteristics upon admission, laboratory data, and clinical outcomes are reported for survivors and nonsurvivors in Table I.40. The mean age for both cohorts was 44 years (range, 18–91 years), 50.5% of the subjects were women, all the patients were Caucasian, and 51.42% had rural residence. The time interval between toxin exposure and presentation to the ED ranged from 0.5 to 6.5 hours.

Table I.40. Baseline patient demographics, clinical and laboratory characteristics, and outcomes.

	Derivation cohort			Validation cohort		
Patients characteristics	Survivors (N=164)	Nonsurvivors (N=16)	*P* value for surviving vs dying	Survivors (N=124)	Nonsurvivors (N=11)	*P* value for surviving vs dying
Demographics and clinical parameters						
Mean age, y (SD)	43 (16.5)	62.1 (14.2)	<0.0001	42.4 (15.7)	60.1 (12.4)	<0.0001
Male/female, %	91.3/90.9	8.7/9.1	0.566	93.8/90.1	6.2/9.9	0.329
Residence (R/U), %	95.6/86.7	4.4/13.3	0.064	97.2/85.7	2.8/14.3	0.024
Poison type, %			0.089			0.450
Combination of poisons	94.3	5.7		93.6	6.4	
Drugs*	94	6		92.3	7.7	
Illicit drugs	100	—		100	—	
Chemicals	80	20		91.7	8.3	
Toxic gases	86.7	13.3		75	25	
Mean ethanol, mg/dL (SD)	57.37 (116.20)	39.81 (65.79)	0.553	63.63 (131.00)	28.91 (90.25)	0.392
Median GCS (IQR)	13 (4)	7 (9)	0.001	13 (5)	5 (9)	0.002
Mean SBP, mm Hg (SD)	124.81 (23.52)	111.13 (38.81)	0.039	125.66 (20.59)	118.27 (33.19)	0.283
Mean DBP, mm Hg (SD)	76.65 (13.35)	65.44 (22.89)	0.003	77.77 (12.99)	73.36 (19.24)	0.304
Mean HR, b/min (SD)	91.83 (23.12)	89.63 (36.52)	0.732	90.05 (21.48)	94.73 (36.49)	0.518
Laboratory tests						
Mean lactate, mmol/L (SD)	2.68 (2.52)	7.10 (5.58)	<0.0001	1.76 (0.81)	3.89 (4.18)	<0.0001
Mean HCO_3, mmol/L (SD)	23.71 (3.98)	14.10 (7.54)	<0.0001	23.44 (3.84)	15.83 (7.69)	<0.0001
Mean Na^+, mmol/L (SD)	140.34 (5.77)	140.63 (5.30)	0.850	141.19 (4.16)	139.18 (6.46)	0.148
Mean K^+, mmol/L (SD)	3.84 (0.52)	4.57 (1.14)	<0.0001	3.59 (0.43)	4.02 (0.99)	0.008
Mean Ca^{2+}, mmol/L (SD)	1.40 (1.30)	1.15 (0.23)	0.458	1.19 (0.4)	1.10 (0.1)	0.477
Mean Mg^{2+}, mg/dL (SD)	1.93 (0.23)	1.94 (0.53)	0.910	1.93 (0.27)	1.99 (0.71)	0.696
Mean creatinine, mg/dL (SD)	0.85 (0.41)	1.21 (0.42)	0.001	0.88 (0.45)	1.09 (0.42)	0.139
Mean glucose, mg/dL (SD)	125.03 (48.50)	192.75 (80.79)	<0.0001	123.06 (52.88)	215.55 (119.72)	<0.0001
Mean Hb, g/dL (SD)	13.73 (1.53)	14.33 (2.27)	0.152	13.68 (1.97)	13.97 (1.84)	0.633
Mean WBC, × 1000 mcgL (SD)	10.07 (4.66)	14.12 (5.68)	0.001	10.60 (5.43)	12.12 (6.06)	0.381
Mean BNP, pg/mL (SD)	65.65 (139.52)	196.66 (152.51)	<0.0001	181.52 (518.57)	214.94 (134.87)	0.858
Mean CKMB, ng/mL (SD)	7.64 (12.25)	13.07 (17.81)	0.012	4.63 (6.24)	13.64 (19.39)	<0.0001
Mean AST, U/L (SD)	38.78 (75.96)	90.13 (92.26)	0.012	35.22 (39.57)	92.18 (108.87)	<0.0001
Mean ALT, U/L (SD)	28.30 (31.73)	52.63 (51.98)	0.007	30.67 (33.62)	54.00 (57.48)	0.042
Mean CK, U/L (SD)	635.99 (4417.51)	757.13 (1578.72)	0.914	521.01 (1258.71)	737.73 (1353.28)	0.601
ECG and TTE parameters						
Mean QTc interval, ms (SD)	412.96 (74.27)	487.46 (138.92)	0.001	381.63 (62.38)	454.55 (163.38)	0.002
Mean LVEF, % (SD)	55.49 (7.19)	43.38 (10.49)	<0.0001	53.00 (7.18)	44.88 (7.50)	0.006
Mean DT, ms (SD)	201.82 (39.85)	249.44 (30.21)	<0.0001	202.51 (35.37)	239.27 (31.39)	0.001
Clinical outcomes						
Need for ICU therapy, %	18.3	62.5	<0.0001	16.9	63.6	0.002
Complications, %			0.001			0.001
Rhabdomyolysis	3	—		3.2	—	
Respiratory	3.7	—		4.8	—	
Cardiovascular	10.4	—		13.7	—	
Hepatic	4.9	—		5.6	—	
Gastro-enteral	1.2	—		1.1	—	
Renal	2.4	—		2.9	—	
CNS	6.1	—		6.5	—	
Multiple	14	100		13.7	100	
Mean length of stay, d (SD)	4.26 (3.27)	6.94 (5.90)	0.005	4.24 (2.88)	5.18 (4.07)	0.319

ALT=alanine transaminase, AST=aspartate aminotransferase, b/min=beats per minute, BNP=brain natriuretic peptide, CK=creatine kinase, CKMB=MB isoenzyme of creatine kinase, CNS=central nervous system, DBP=diastolic blood pressure, DT=E wave velocity deceleration time, ECG=electrocardiogram, GCS=Glasgow Coma Scale, Hb=hemoglobin, HCO3=bicarbonate, HR=heart rate, ICU=intensive care unit, LVEF=left ventricle ejection fraction, OTC=over-the-counter, R=rural residence, SBP=systolic blood pressure, SD=standard deviation, U, urban residence, WBC, white blood cells, TTE, transthoracic echocardiography. * Included prescription drugs and OTC.

The leading cause of poisoning was acute exposure to a combination of poisons (29.4% in the derivation cohort and 34.8% in the validation cohort, respectively).

Among the patients in the derivation cohort, the drugs most frequently involved were: sedative hypnotics (13.9%); illicit drugs, including opiates (5%); antidepressants (3.9%); anticonvulsants (3.9%); cardiovascular medication (3.9%); NSAIDs, including salicylates (3.9%); antipsychotics (2.8%); and acetaminophen (2.8%) – table I.41. The distribution of nonpharmaceutical poisons (table I.41) was as follows: pesticides and herbicides (11.7%); carbon monoxide (8.3%); toxic alcohols, other than ethanol (5%); other chemicals, such as

formaldehyde or hydrocarbon mixtures (2.2%); and rat poison (1.2%). The majority of the cases were due to self-poisoning, with only 23 cases (7.3%) being accidental poison exposures. The overall in-hospital mortality rate was 8.57% (n=27), providing an adequate number of events to evaluate predictors.

Table I.41. Xenobiotics involved in the acute poisoning.

Derivation cohort (180 patients)	Poison involved	N	Percent	Validation cohort (135 patients)	N	Percent
	Ethanol co-ingestion	74	41.1		48	35.6
	Combinations (multiple drugs; drug-toxin)	53	29.4		47	34.8
	Single agent exposure				**Single agent exposure**	
	Acetaminophen	5	2.8		1	.7
	Salicylates	4	2.2		1	.7
	NSAID's	3	1.7		-	-
	COX-2 inhibitors	1	.6		-	-
	Antidementia drugs	2	1.1		1	.7
	Benzodiazepines	13	7.2		8	6
	Barbiturates	5	2.8		1	.7
	Miscellaneous anxiolytics, sedatives and hypnotics	7	3.9		2	1.5
	Antipsychotics	5	2.8		3	2.2
	Antidepressants	7	3.9		9	6.7
	Cardiovascular drugs (CCBs, BBs, digitalis glycosides, ACEI)	7	3.9		8	6
	Antiepileptics	7	3.9		3	2.2
	Drugs of abuse (cannabis, ethnobotanicals, ecstasy, heroin)	7	3.9		5	3.7
	Narcotic analgesics	2	1.1		2	1.5
	Cocaine	1	.6		-	-
	Ethylene glycol	4	2.2		9	6.7
	Methanol	5	2.8		8	6
	Isoniazid	1	.6		-	-
	Organophosphate compounds	11	6.1		10	7.4
	Organochlorine compounds	6	3.3		5	3.7
	Miscellaneous pesticides & herbicides	4	2.2		2	1.5
	Rat poison	1	.6		-	-
	Hydrocarbon mixtures	2	1.1		1	0.7
	Formaldehyde	2	1.1		1	0.7
	Toxic gases and fumes	15	8.3		8	6

NSAID's, non-steroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; CCBs, calcium channel blockers; BBs, beta-blockers; ACEI, angiotensin-converting enzyme inhibitor.

Treatment received in the emergency room

Thirty-seven (20.6%) patients in the derivation cohort received a specific antidote therapy, 46 (25.6%) patients were treated by activated charcoal, and 2 (1.1%) had a gastric lavage. Ninety-five (52.8%) patients didn't receive an antidote therapy (either non-existing antidote or unavailable specific antidote in our country). Among the 16 non-survivors in the derivation cohort, 6 patients received an antidote therapy. Out of the 11 non-survivors in the validation cohort, 4 patients received an antidote therapy.

Non-survivor patients

In derivation cohort, 4 patients were poisoned with toxic alcohols (2 methanol, 2 ethylene glycol), 3 patients were poisoned with multiple xenobiotics (antidepressants with benzodiazepines, multiple cardiovascular drugs, and pesticides with antipsychotics), two

deaths were recorded after lamotrigine poisoning, 2 patients died after carbon monoxide exposure, and two after formaldehyde exposure, followed by acute poisoning with antidepressants, organophosphate pesticides and sedative-hypnotic, each with a case.

In validation cohort, 3 patients were intoxicated with combination of poisons (antidepressants, cardiovascular drugs, and pesticides with formaldehyde), 2 patients were exposed to a toxic alcohol (ethylene glycol), two patients died after acute carbon monoxide exposure, three deaths were recorded after prescription medication poisoning (one with antidepressants, one with lamotrigine, and one with calcium-channel blockers) and one after organophosphate pesticide exposure.

The direct cause of death was multiple complications involving at least 2 vital organs (dysrhythmias, toxic-induced myocardial injury, refractory shock, acute respiratory distress syndrome, and multiple organ failure). In both cohorts, deaths were recorded in patients with acute poisoning involving chemicals (10 patients; 3.2%), drugs (7 patients; 2.2%), a combination of poisons (6 patients; 1.9%), and toxic gases (4 patients; 1.3%).

Univariable and multivariable analysis

Out of the 180 patients of the derivation cohort, there were 16 nonsurvivors (8.89%). Univariable predictors of in-hospital mortality are shown in Table I.42.

Table I.42. Selected factors using univariate analysis for building the model.

Characteristics	Wald χ^2	Odds ratio	95% CI	*P* value
Age	14.528	1.070	1.034–1.108	<0.0001
Urban residence	4.000	0.302	0.094–0.976	0.046
GCS $\leq$ 8	7.703	0.224	0.078–0.644	0.006
PSS $\geq$ 3	10.710	0.111	0.030–0.414	0.001
SBP	4.246	0.977	0.956–0.999	0.039
DBP	7.989	0.949	0.916–0.984	0.005
Lactate	18.582	1.310	1.159–1.481	<0.0001
HCO_3	24.383	0.735	0.651–0.831	<0.0001
K^+	14.954	4.041	1.991–8.200	<0.0001
CRP	5.016	1.087	1.010–1.169	0.025
Creatinine	3.901	3.378	1.009–11.307	0.048
Glucose	14.823	1.016	1.008–1.024	<0.0001
WBC	8.734	1.143	1.046–1.249	0.003
RDW	6.056	1.541	1.092–2.175	0.014
BNP	8.427	1.004	1.001–1.006	0.004
CKMB	5.960	1.073	1.014–1.136	0.015
ALT	5.230	1.012	1.002–1.022	0.022
QTc interval	8.815	1.010	1.003–1.016	0.003
DT	14.253	1.031	1.015–1.047	<0.0001
LVEF	20.107	0.836	0.773–0.904	<0.0001

ALT=alanine transaminase, BNP=brain natriuretic peptide, CI=confidence interval, CKMB=MB isoenzyme of creatine kinase, CRP=C reactive protein, DBP=diastolic blood pressure, DT=E wave velocity deceleration time, GCS=Glasgow Coma Scale, HCO3=bicarbonate, K+=potassium, LVEF= left ventricle ejection fraction, PSS=Poisoning Severity Score, RDW=red cell distribution width, SBP=systolic blood pressure, WBC=white blood cells.

On multivariable analysis, only 6 of the 20 candidate variables remained predictive of mortality (Table I.43). The following variables independently correlated with mortality: age, lactate upon ED presentation, potassium (K+), initial MB isoenzyme of creatine kinase (CKMB) upon ED arrival, the QTc interval on initial ECG, and the E wave velocity deceleration time (DT) on the echocardiography performed in the ED. Although other variables (including, urban residence, glucose level, and left ventricular ejection fraction) were

predictive for mortality on univariable analysis, these were not included in the final model because the association was not statistically significant. Blinded duplicate assessments were performed in 20 patients (researcher only: 7 patients; physician only: 10 patients; both physician and researcher: 3 patients), and there were no statistically significant differences in the inter-examiner assessments.

Table I.43. In-hospital mortality model.

Variable	Wald χ^2	Odds ratio	95% CI	*P* value
Age	7.325	1.109	1.029–1.196	0.007
Gender (male)	2.617	4.418	0.730–26.727	0.106
QTc interval	4.696	1.010	1.001–1.019	0.030
DT	6.916	1.028	1.007–1.049	0.009
CKMB	3.125	1.051	0.995–1.110	0.077
Lactate	11.412	1.579	1.211–2.058	0.001
K^+	9.313	6.783	1.984–23.194	0.002

CKMB=MB isoenzyme of creatine kinase, DT=E wave velocity deceleration time, K+=potassium.

Nomogram development

Binary logistic regression analysis indicated that death probability in acute poisoning can be estimated using the following 6 significant predictor variables: age, initial lactate, K+, initial CKMB, the QTc interval, and DT. We added gender as a further demographic characteristic (Table I.44), to use the same nomogram for male and female patients. ROC curves had validated discriminatory power of predictive variables for mortality.

Table I.44. The risk-prediction nomogram.

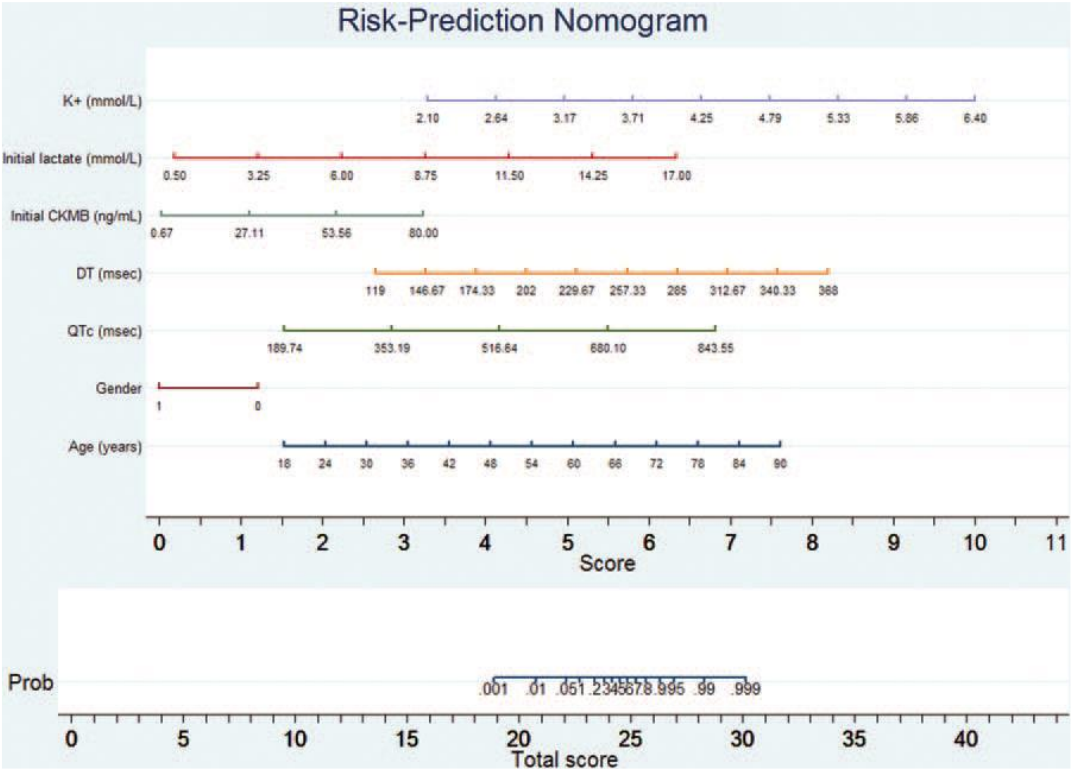
Death	Odds ratio	Standard error	z	$P>\|z\|$	[95% Conf. interval]
Age	1.109299	0.0425151	2.71	0.007	1.029024– 1.195837
Gender	0.2263626	0.2078961	−1.62	0.106	0.0374148– 1.369512
QTc interval	1.009945	0.0046119	2.17	0.030	1.000946– 1.019025
DT	1.027673	0.0106673	2.63	0.009	1.006977– 1.048794
CKMB	1.05087	0.0294963	1.77	0.077	0.9946195– 1.110301
Lactate	1.578846	0.2134442	3.38	0.001	1.21134– 2.05785
K^+	6.782769	4.254872	3.05	0.002	1.98355– 23.19375
Constant	4.02e-13	2.82e-12	−4.07	0.000	4.27e-19– 3.79e-07
Log likelihood = −20.915427					
Number of obs = 180					
LR χ^2 (7) = 66.15					
Prob. > χ^2 = 0.0000					
Pseudo R^2 = 0.6126					

CKMB=MB isoenzyme of creatine kinase, DT=E wave velocity deceleration time, K+=potassium.

The areas under the curves were: DT 0.84 (95% CI 0.74–0.94, P<0.001); age 0.80 (95% CI 0.70–0.91, P<0.001); initial lactate 0.74 (95% CI 0.58–0.90, P=0.002); initial CKMB 0.69 (95% CI 0.57–0.81, P=0.012); QTc interval 0.68 (95% CI 0.53–0.83, P=0.018); K+ 0.66 (95% CI 0.47–0.84, P=0.038). This analysis indicated that all predictor variables had good discriminatory power. The following variables had a high value of AUC, predicting mortality with excellent discrimination (AUC > 0.80): DT (cutoff point 232 msec; sensitivity of 87.5% and a specificity of 79.9%) and age (cutoff point 53 years; sensitivity of 87.5% and a specificity of 72%). Using the 6 independent risk factors, in addition to sex, we developed a nomogram that predicts in-hospital mortality (Table I.44).

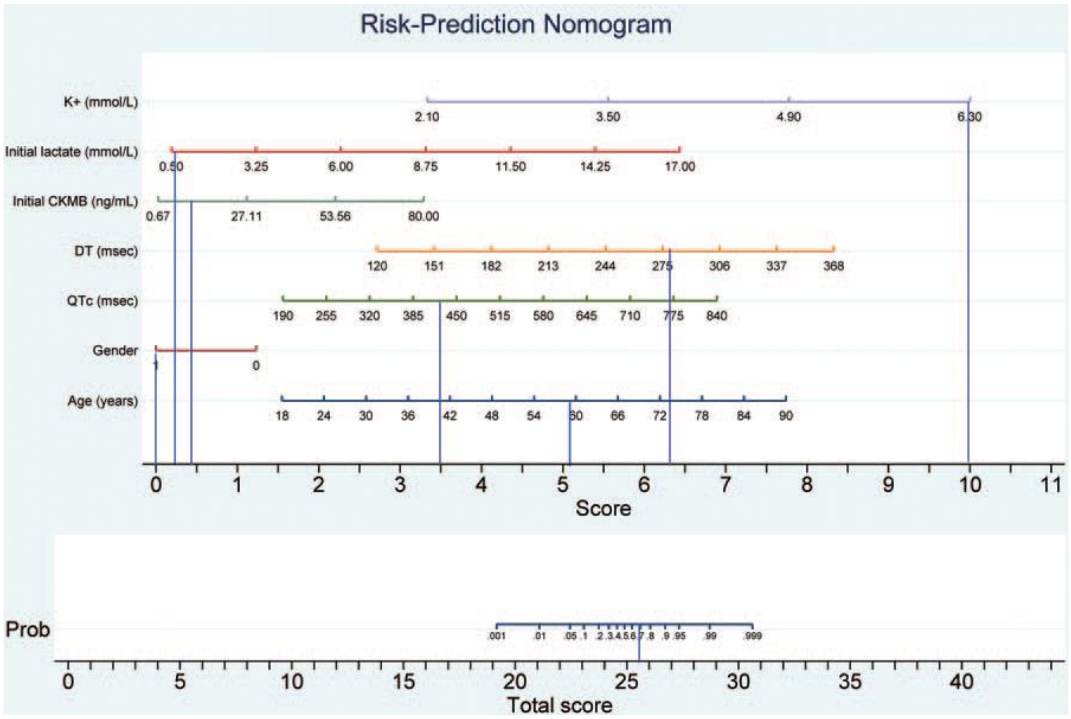
The nomogram was characterized by 1 scale corresponding to each variable, a score scale, a total score scale, and a probability scale (Figure I.33). The use of the nomogram is simple, and involves 3 steps. First, on the scale for each variable, the value corresponding to a specific patient is read and the score scale is used to calculate the scores for all variable values. Second, the total score is calculated by adding up all the scores obtained in the previous step, and its value is identified on the total score scale. Finally, the probability of an event corresponding to the total score of the subject is read on the probability scale.

For example, 2 unconscious patients were admitted to the ED after acute exposure to an unknown quantity of toxic alcohol. There were no available data regarding the time from poison exposure to ED presentation, and the serum levels of toxic alcohol could not be assessed in the ED. Clinical management was comparable in these cases: both patients were admitted to the ICU and received antidote therapy with ethanol (the only available antidote for toxic alcohol poisoning at that time), underwent hemodialysis for toxin removal, and received supportive therapy. However, the outcomes were different. The first patient died after 9 days in the ICU, the second patient was transferred to the medical ward after 1 day, and discharged home 2 days later. The application of the nomogram to the first patient (Figure I.34. a) showed a total score of 25.5, with a death probability of 0.68. The death probability calculated using the nomogram was identical to the one estimated by using logistic regression model. The first patient did not survive. The same methodology was applied to the second patient showing a significantly lower death probability; the second patient survived (Figure I.34.b).

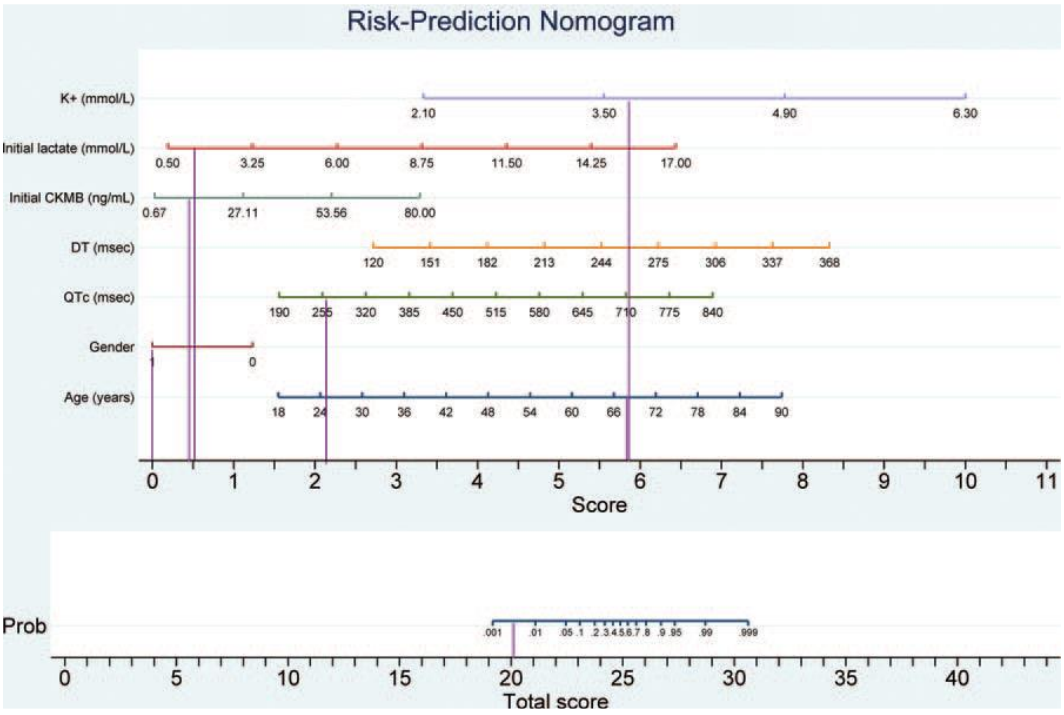


The risk-prediction nomogram for mortality in acute poisoning with drugs and nonpharmaceutical agents incorporating age (y), sex (1 male, 0 female), QTc interval (msec), DT (msec), initial CKMB (ng/mL), initial lactate levels (mmol/L), and K+ levels (mmol/L). CKMB=MB isoenzyme of creatine kinase, DT = the E wave velocity deceleration time, QTc = corrected QT interval.

Figure I.33. Risk-prediction nomogram for mortality in acute poisoning.



a. Non-survivor: A line is drawn downward from the value of each category to the score line. The points are then added to determine the total score, and a line is drawn upward to find the risk of mortality. Death probability estimation: K+ (mmol/L): 6.3 _ score = 10; initial lactate (mmol/L): 0.9 _ score = 0.2; initial CKMB (ng/mL): 7.94 _ score = 0.4; DT (msec): 278 – score = 6.3; QTc (msec): 427.36 – score =3.5; sex: 1 (male) – score = 0; age (y): 59 – score =5.1. Total score = 25.5, with a death probability of 0.68.



b. Survivor: Death probability estimation: K+ (mmol/L): 3.7 _ score=5.8; initial lactate (mmol/L): 1.3 _ score=0.5; initial CKMB (ng/mL): 7.3 _ score=0.4; DT (msec): 251 – score=5.6; QTc (msec): 258.7 – score= 2.1; sex: 1 (male) – score=0; age (y): 68 – score=5.8. The total score = 20.2, with a death probability of 0.004.

Figure I.34. Example of the use of risk-prediction nomogram in 2 patients with acute poisoning from toxic alcohol.

The nomogram was evaluated as a diagnostic test calculating sensitivity, specificity, and positive and negative likelihood ratios. The final model was internally validated using bootstrap resampling (Harrell, 2010). Receiver-operating characteristic analysis indicated that the accuracy of the predicted probability for the model was 97.6% compared with 84% or less, when using a single variable (Table I.45).

Table I.45. The AUC of the ROC curves for the nomogram and variables from logistic regression model in derivation and validation cohort.

	Derivation cohort			Validation cohort		
	AUC	95% CI	*P* value	AUC	95% CI	*P* value
Nomogram variable	0.976	0.954–0.998	<0.001	0.949	0.879–1.000	<0.001
Age	0.803	0.702–0.905	<0.001	0.805	0.689–0.922	0.001
QTc interval	0.679	0.526–0.831	0.018	0.664	0.450–0.878	0.072
DT	0.841	0.737–0.944	<0.001	0.787	0.673–0.900	0.002
CKMB	0.690	0.572–0.809	0.012	0.757	0.632–0.882	0.005
Lactate	0.737	0.577–0.898	0.002	0.657	0.474–0.840	0.085
K^+	0.658	0.471–0.844	0.038	0.606	0.372–0.841	0.244

AUC=area under the curve, CKMB=MB isoenzyme of creatine kinase, DT=E wave velocity deceleration time, K+=potassium, ROC=receiver operator characteristic.

Nomogram use in the stratification of patient risk

There were 135 patients and 11 deaths in the validation cohort (8.14% mortality rate). The nomogram was used to assess the risk of mortality for all patients in the validation cohort; the probability indicated by the nomogram was then compared with the probability using the model developed. The AUC for the nomogram was 0.95 (95% CI, 0.88–1, P<0.0001), and the AUC for the model was 0.96 (95% CI, 0.89–1, P<0.0001; Figure I.35), which proved that our logistic regression model and nomogram had superior capability in predicting mortality.

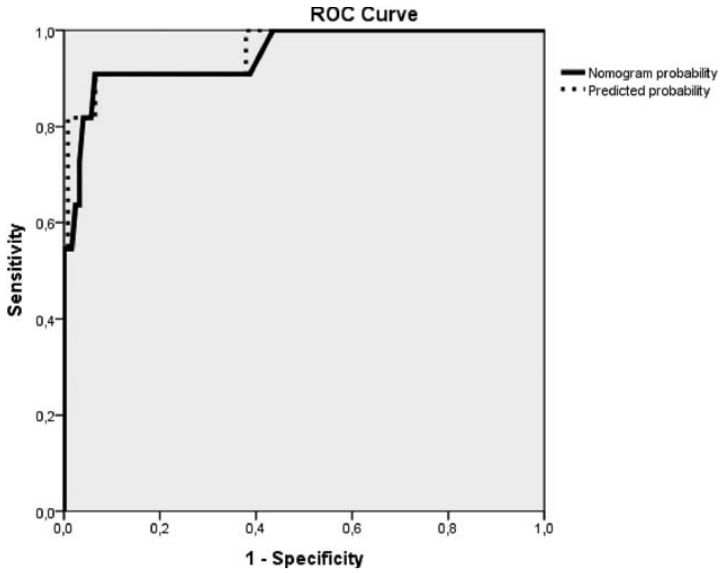


Figure I.35. ROC curves validate the power of the nomogram in the validation cohort.

For high-risk patients (total score > 24 points), the sensitivity was 90.9%, the specificity was 93.5%, the PPV 100%, and the NPV 96%. For low-risk patients (total score ≤ 24 points), the sensitivity was 81.8%, the specificity was 96%, the PPV 96%, and the NPV 100%.

Discussion

To our knowledge, our model is the first risk-prediction nomogram attempting to evaluate in-hospital mortality in patients with acute poisoning. In the field of toxicology, the nomograms currently available are used for the identification of the benefits of antidote therapy in acetaminophen-poisoning and for toxicity or arrhythmia risk assessment, with some nomograms also used in clinical practice (Dugandzic et al., 1989; Rumack, 2002; Chan et al., 2007). There have been recent attempts to generate a nomogram for choosing the appropriate duration of hemodialysis in acute methanol poisoning (Lachance et al, 2015).

A nomogram is a graphical representation of a mathematical formula or algorithm incorporating several predictors modeled as continuous variables to predict an end-point, based on traditional statistical methods, such as multivariable logistic regression and Cox proportional hazards analysis (Kuo et al., 2013). The non-representational messages in multiple regression models are rendered more intuitive and easily applicable to computation by nomogram. Nomograms are extensively used in various clinical settings to predict the probability of an event. As early as 1975, Rumack and Matthew had developed a famous nomogram in acetaminophen poisoning. A nomogram is beneficial to emergency medicine physicians for evaluating patients immediately, especially in rural areas. Predictive nomograms may be used in optimally estimating individualized disease-related risks that simplify patient management-related decision making. This user-friendly instrument could be applied by physicians to enhance patient management and to eventually reduce mortality. Nomograms also provide superior individualized disease-related risk estimations that facilitate patient management-related decisions. Nomograms are currently the most accurate available tools, with the greatest discriminating characteristics for predicting outcomes in patients with different oncologic pathologies (Kuo et al., 2013; Zhou et al., 2015; Shariat et al., 2008), or in patients with heart failure (Abraham et al., 2008).

In the present study, we developed a predictive model incorporating demographic, ECG and echocardiography parameters, as well as laboratory data, from a cohort of patients with acute poisoning with different toxins, to determine the mortality risk on admission to the ED. The significant independent covariates for the mortality risk in the present study were age, DT as a measure of impaired LV diastolic function, initial lactate level, CKMB as a marker of myocardial injury, the QTc interval, and the potassium level. Furthermore, we used sex as a categorical variable. Using these factors, we constructed a nomogram providing more precise, simple, and rapidly available risk-analysis information for individual patients acutely exposed to a poison, irrespective of type (drug, chemical, or gas), toxicokinetics, dosage, and route of entry. The information is based on objective markers, such as laboratory tests and imaging parameters, and not on clinical scales which may be applied subjectively by physicians according to different levels of expertise. In cases of acute poisoning involving unresponsive patients in the ED, with no knowledge of the type, dose, or serum levels of the offending toxin, this predictive nomogram may aid emergency physicians to identify high-risk patients more promptly, enabling the administration of specific or aggressive therapy, or the immediate referral of the patient to an ICU with advanced capacity, to reduce mortality. Nomogram use may not only facilitate early management decision making, but may also minimize unnecessary tests and expenses. In the example presented in the Results section, the use of the nomogram in the ED would have identified, on admission, the patient with a low risk of death, and would have helped to choose a different approach, for example, admission to a non-ICU ward and avoidance of hemodialysis.

The in-hospital mortality predictors detected in our model are consistent with other published reports of patients hospitalized with acute poisoning. Retrospective studies found that prolonged QTc interval, older age, increased arterial lactate upon admission, or myocardial

injury were associated with in-hospital mortality following exposure to different types of poison (Kim et al., 2014; Liu et al., 2013; Mégarbane et al., 2010; Manini et al., 2010; Kao et al., 2009). Our previous research showed that there are objective indicators, available in the ED, that can predict a poor outcome in patients exposed to systemic poisons, such as cardiac biomarkers, and lactate (Lionte et al., 2017). In this prospective study, we confirmed the predictive role for death of increased age, initial lactate level, CKMB, and prolonged QTc interval; we also identified new variables, such as DT, and K+ levels, which accurately predicted the mortality risk. These findings confirm the relevance of these variables as prognostic factors in a representative sample of the population with acute poisoning due to a range of toxins.

Acute poisonings represent a problem in both developed and developing regions worldwide. In Romania, epidemiological data suggest that acute drug poisoning in suicide attempts is the most common reason for hospitalization of patients with poisoning (97.27%) and poisoning more frequently occurs due to a combination of drugs (32.92%), with a mortality rate of 0.3% (Sorodoc et al. 2011). Self-poisoning with organophosphate pesticides in our area showed a mortality rate of 3.8% (Gazzi et al., 2015). Most of the patients in our study with acute poisoning had attempted suicide, using drugs or a combination of poisons, comparable with the distribution reported in studies from the United States, or Central Europe (Dart et al., 2015; Krakowiak et al., 2011).

High troponin levels have been reported to be associated with an increased mortality risk in acute drug poisoning (Manini et al., 2016), although this finding could not be corroborated by our model. However, the number of patients with readings above the normal range may not have been sufficiently large to detect any evidence of this association after acute exposure to heterogeneous drugs and nonpharmaceutical agents.

Our results confirmed that the parameters assessing early acute myocardial injury, such as prolonged DT, which reflects diastolic dysfunction, are predictive of mortality. This is consistent with the findings reported for carbon monoxide poisoning, where diastolic dysfunction precedes systolic dysfunction of the left ventricle, even in the absence of ECG changes (Çiftçi et al., 2013; Davutoglu et al., 2006).

We also found that potassium levels have a potential role in mortality risk-prediction in patients with acute poisoning, contrary to previous research on self-poisoning with different types of medication which failed to demonstrate that abnormal K+ levels were a life-threatening event requiring emergency treatment and/or ICU admission (Reydel et al., 2016). This finding may be explained by the heterogeneity of the poisons used and the proportion of nonpharmaceutical agents (33.3%) in our cohort. However, researchers have demonstrated that an increased in-hospital mortality rate is significantly associated with severe underlying disease and coexisting medical conditions, as well as with a severe increase in K+ levels (An et al., 2012).

Although hyperglycemia is not a common feature of overdose (Jones et al., 2016), the admission levels of blood glucose following acute poisoning may be associated with clinical outcome (Sabzghabaee et al., 2011). The association between glucose levels and mortality in patients with organophosphate and methanol poisoning has been proven (Gunduz et al., 2015; Shadnia et al., 2013). We did not include glucose levels in the nomogram, based on the results of multivariate analysis.

The mortality rate in our cohort was comparable to that on reported in other prospective observational studies (9.7%) poisoning due to a combination of drugs (Eizadi Mood et al., 2011), and lower than pesticide-related fatalities (25.31%) reported in retrospective studies (Hsu et al., 2013). However, our mortality rate was higher than that reported in 2012 by the American Association of Poison Control Centers, concluding that only 1% of fatalities were

exposure-related (Mowry et al., 2014). A possible explanation for the higher fatality rate in our cohort could be the fact that some antidotes are unavailable in our country, such as 4-methylpyrazole (for toxic alcohols), and Digoxin Immune Fab (for digitalis glycosides).

Our results demonstrated the benefits of the nomogram used as a decision making-support tool by emergency physicians in patients with acute poisoning with drugs and nonpharmaceutical agents. This risk-prediction nomogram may have an advantage over traditional tools, such as GCS, PSS, or other clinical scores, because the association between predictors (age, sex, QTc interval, DT, CKMB, lactate and K+) and the predicted variable (death) is visible at a glance. This advantage may be particularly useful in areas where the nomogram user can choose the values of the covariates (e.g., a physician making management decisions involving several factors).

Some limitations of this study should be mentioned. First, the data were collected from a single tertiary center. Findings from our study may not be generalizable to other populations of patients with acute poisoning, although the epidemiological data in our area are consistent with those reported in different regions of the world (Dart et al., 2015; Krakowiak et al., 2011). Second, this was an observational study, so it is possible that there are unmeasured systematic biases that are specific to the region. However, there is no a priori reason to assume that local practices or facilities differ substantially from elsewhere, and demographic effects are incorporated in the nomogram itself. It is reasonable to assume that the nomogram can be broadly applicable, at least within a nondiabetic adult population with acute poisoning with drugs and nonpharmaceutical agents. Third, further nomograms, as well as improvements in existing nomograms, are required, as none of the existing nomograms are able to make predictions with perfect accuracy. We could not account for the impact of the time to ED presentation, after acute exposure, the toxicokinetics, and the serum poison level on mortality in our cohort. We did not use a simplified model without including DT, despite the fact that performing bedside echocardiography on admission may be difficult in some EDs. Finally, no data on outcome after hospital discharge were available, and death occurring after discharge may have been missed. Novel biomarkers, larger data sets, improved data collection methods, and more sophisticated modeling procedures are needed to improve predictive accuracy. We intend to continue the research to validate this nomogram in a separate prospective trial, involving a larger dataset of patients with acute poisoning and including poison with local effects, as well as diabetic subjects.

Conclusions

We developed a 7-variable risk-prediction nomogram based on demographic, routine laboratory tests, and ECG and echocardiography parameters, which accurately predicts the probability of in-hospital mortality for nondiabetic subjects acutely exposed to drugs and nonpharmaceutical agents, exclusively from the objective tests available in the ED. This nomogram used in cases of acute poisoning with drugs and non-pharmaceutical agents has the potential to identify high-risk patients upon presentation to the ED. Further research is required to demonstrate how this nomogram applies to other populations (for example, to subjects under 18 years, different ethnic groups, and patients with caustic exposure) and to elucidate how the incorporation of this tool into clinical practice improves the care or use of resources in patients with acute poisoning.

II. THE ROLE OF MODERN THERAPIES IN THE MANAGEMENT OF ACUTE POISONING

During the stabilization and diagnostic phase, some complications may require specific interventions. Antidotes are a critical component in the care of poisoned patients. Unfortunately, only 5% of poisons have a specific antidote (Lionte & Sorodoc, 2009). Specific antidotes that neutralize or prevent the toxic effect of certain drugs are available, but the antidote expert panel recommended the consideration of 24 antidotes for emergency stocking by facilities that provide emergency care (Dart et al., 2009).

Measures to enhance elimination of drugs and toxins are a desirable goal, but rapid elimination of most drugs and toxins is not practical most of the time and may be unsafe for the patient. Before applying these techniques, one must ask which patients are candidates for this, if the drug or toxin is accessible for the removal procedure, and which method to use (Olson, 2004). Lipid resuscitation therapy (LRT), lipid emulsion therapy (LET) or intravenous lipid emulsion (ILE) therapy refers to the administration of a lipid emulsion with the intent of reducing the clinical manifestations of toxicity from excessive doses of certain medications. LET was proved beneficial in several case reports of beta-blocker and calcium channel blocker overdose, but there are no human studies about the use of intravenous lipid emulsion in b-blocker overdose. Animal studies showed that Intralipid® reduces QRS duration and improves bradycardia and hypotension in propranolol toxicity. LET has recently been recommended by Toxbase in patients with a history of beta blockers overdose, who have cardiotoxic symptoms that are not responsive to standard treatment, and also by the American College of Medical Toxicology, in overdose with lipid-soluble cardiotoxic medications, for "patients with hemodynamically instability, not responsive to standard resuscitation measures, such as fluid replacement, inotropes, and pressors, where appropriate" (Tabone & Ferguson, 2011; ACMT, 2011). Intravenous lipid therapy is a plausible and effective therapy for massive calcium channel blocker overdose, and could be considered early in patients presenting with hemodynamic compromise (Su & Weiselberg, 2010; Liang et al., 2011).

II.1. The role of lipid emulsion therapy in the management of patients poisoned with cardiovascular drugs.

This direction of research is reflected in the following published articles:

1. Bologa, C**; Lionte, C *(corresponding author)***;** Popescu, A; Sorodoc, V; Sorodoc, L. First Case of Acute Poisoning with Amiodarone and Flecainide in Attempted Suicide Successfully Managed with Lipid Emulsion Therapy in the Emergency Department: Case Report and Literature Review. *Healthcare* 2021; 9(6): Article Number 671 DOI 10.3390/healthcare9060671 (**IF 2.645**)
2. Bologa, C; **Lionte, C**; Coman, A; Sorodoc, L. Lipid emulsion therapy in cardiodepressive syndrome after diltiazem overdose-case report. *Am J Emerg Med* 2013; 31(7): 1154.e3–1154.e4. (**IF 1.704**)

Background

The intravenous lipid emulsion was initially designed to treat cardiotoxicity induced by intravascular injection or local anesthetic overdose (Cave & Harvey, 2009; Bologa et al., 2013). Anesthesiologists have primarily used intravenous fat emulsion rescue therapy for local anesthetic toxicity (e.g., bupivicaine), and more recently, its use has been reported in betablocker and calcium channel blocker (CCB) toxicity. There are multiple human case

reports in which LET appears to have contributed to recovery from cardiogenic shock or arrest (Stellpflug et al., 2010; Jamaty et al., 2010).

LET is composed of triglycerides and a phospholipid emulsifier, and was recently used as an antidote, because it attenuates the cardiotoxic effects of some lipophilic drugs (Young et al., 2009). Mechanisms in reversing drug-induced cardiac toxicity are mainly the extraction or sequestration of the lipophilic drugs intravascularly, making them less available to cardiac tissue, the improvement of ischemic myocardial function by shifting energy sources back to fatty acids (the role of metabolic antidote) and a direct reverse of CCB toxicity by activating calcium channels in the heart (Tomaszewski, 2009). The main indications are verapamil overdose, together with hyperinsulinemia/euglycemia **(**HIE), after HIE has failed, refractory shock from CCBs, or other cardiotoxins, in patients who do not respond to other means of treatment, or during cardiac arrest, and life-threatening arrhythmias unresponsive to the above therapies such as ventricular tachycardia (VT), fibrillation, heart block, and asystole (Su et al., 2010; Liang et al., 2011; Tomaszewski, 2009; Plumb et al., 2011). The described adverse effects are: anaphylactoid reaction, subacute reactions or the "fat overload syndrome" (i.e., coagulopathy, jaundice, lipid accumulation in the liver), and interference with laboratory studies (Su et al., 2010).

Overdoses with cardiovascular drugs are associated with significant morbidity and mortality, thus catching the attention of the practitioners. CCBs and beta-blockers represent two of the most important classes of cardiovascular drugs involved in producing cardio-depressive syndrome (Sheperd, 2006; Tintinalli et al., 2011; Olson et al., 2005). Antiarrhythmic drugs are widely used in clinical practice. Antiarrhythmic drug therapy carries an understood risk for toxic side effects, even with therapeutic doses. Flecainide induces VT, which is often resistant to direct current cardioversion because the intense sodium channel blockade increases the voltage threshold for cellular depolarization (Banavalikar et al., 2018). Amiodarone prolongs the QT interval, causes conduction disturbances and VT. Amiodarone is also related to exacerbations of VT and an increased defibrillation threshold (Lin et al., 2003; Forgoros, 1984). A combination of these two antiarrhythmics in intentional overdose could lead to dramatic cardiotoxicity. A review of the literature showed no report of a case with a poisoning including an association of amiodarone and flecainide. We found only two case reports of amiodarone intentional overdose: the first case was of a patient who ingested 8,000 mg amiodarone in a suicide attempt, where the blood concentration was 1.1 mg/L, managed with supportive measures; the second case was of a patient with mixed overdose of amiodarone, diltiazem and metoprolol, with a serum level of amiodarone of 2.7 mg/L, in need of ICU therapy (Bonati et al., 1983; Stellpflug et al., 2011). In flecainide overdose, there is a need for exceptional therapeutic interventions both in the ED and ICU (Reynolds & Judge, 2015; Mandawat et al., 2015; Yasui et al., 1997; Auzinger & Scheinkestel, 2001).

Aim of the research

We undertook the present study with the goal of reviewing the reports of amiodarone and flecainide acute poisoning in humans, as well as CCBs, poisoning, with evidence of ED therapies used, their effect, and failure as a treatment for poisoning. We aimed to distinguish which variables might explain failures and successes in either time of administration, substances, or toxic load.

Results

An extensive search of the literature was performed with the journal search engines Thompson ISI—Web of Science, EMBASE, EBSCO, Scopus and PubMed. We used the MeSH terms suicide, amiodarone, flecainide, AND overdose, intoxication, or poisoning in

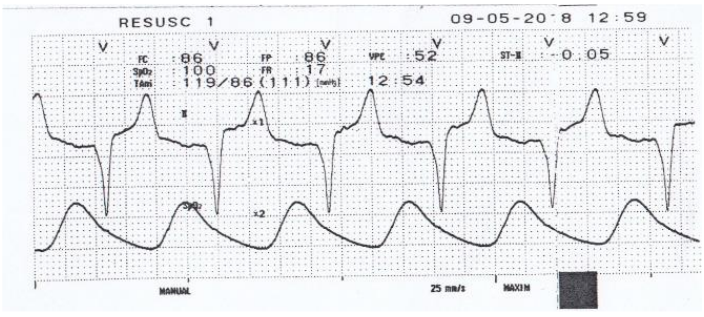
different permutations. Additionally, we examined the citations of all resulting articles for any additional relevant references. Each article was reviewed, and case reports, which included and pictured a 12-lead ECG performed during intoxication, as well as references to intentionality of the poisoning, time to hospital admission, dosage and/or serum level, therapy administered and setting, were included for analysis. The exclusion criteria were: animal and in-vitro studies, forensic and analytical studies, original articles that were not in the English language, as well as comments, editorials, posters, abstracts and letters to the Editor. Those articles reporting flecainide or amiodarone accidental medication errors, and reports with incomplete data were also excluded.

We report the case of a patient who attempted suicide by ingesting a large dose of amiodarone and flecainide, with an ECG depicting signs of cardiotoxicity and ventricular arrhythmias, which was managed successfully in the ED, after hypertonic sodium bicarbonate administration and initiation of LET. A 47-year-old patient was admitted to the ED for fatigue, anxiety, headache. The patient declared the ingestion of 2,000 mg amiodarone and 5,000 mg flecainide in a suicide attempt, 5 h prior to ED arrival. Glasgow Coma Scale score was 12, BP 110/80 mmHg, heart rate 71 bpm. The patient had an episode of atrial fibrillation converted to sinus rhythm with flecainide two years before, had been subjected to a radiofrequency catheter ablation with the isolation of the pulmonary veins one year earlier for atrial flutter, with successful restoration and maintenance of sinus rhythm, and took amiodarone 100 mg daily since. He had a history of depression, but he had quit the specific therapy for several months. During transportation, the monitor recorded a sinus rhythm of 86/min, a prolonged PR interval 240 msec with a normal QRS complex (Figure II.1).

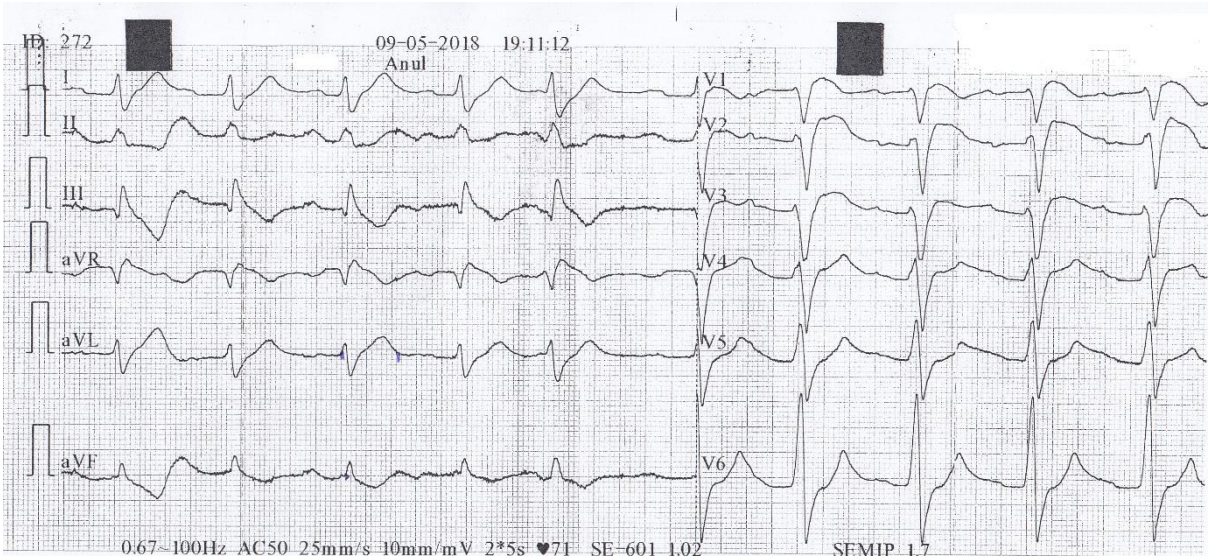
He was first admitted to a local hospital, where he received an initial dose of activated charcoal and normal saline solution, then referred to our ED for specific therapy. The ECG recorded upon first medical contact showed an irregular rhythm, a first-degree atrioventricular (AV) block with a wide QRS complex.

Upon admission to our ED, arterial blood gases (ABG), liver and kidney panel, alkaline phosphatase and LDH were normal, WBC 12.000/mmc, blood glucose 170 mg/dL, and urine toxicological screen negative. Cardiac ultrasound excluded a structural disease. Cardiac biomarkers were within normal range. Given the large dose of antiarrhythmics ingested, we began sodium bicarbonate 8.4% administration, up to 500 mEq/L (Table II.1).

A second ABG showed pH 7.53 and a sodium concentration >150 mEq/L. We initially administered 1 g/kg activated charcoal, followed by 25 g every 4 h for 12 h, to reduce the gastrointestinal absorption of flecainide and increase the elimination of amiodarone, which enters in an enteral-hepatic circuit (Lewin, 2002; Benowitz, 2012).



a. Monitor recording during transportation to the first hospital shows a sinus rhythm of 86/min, a prolonged PR interval of 240 msec with normal QRS complex of 110 msec.



b. 12-lead ECG recorded in the local hospital, 3 h after the ingestion of drugs, shows irregular sinus rhythm of 71/min, with a prolonged PR interval of 280 msec, a wide QRS complex of 160 msec, and slightly prolonged QTc interval of 479 msec.

Figure II.1. The first ECG changes suggestive for toxicity.

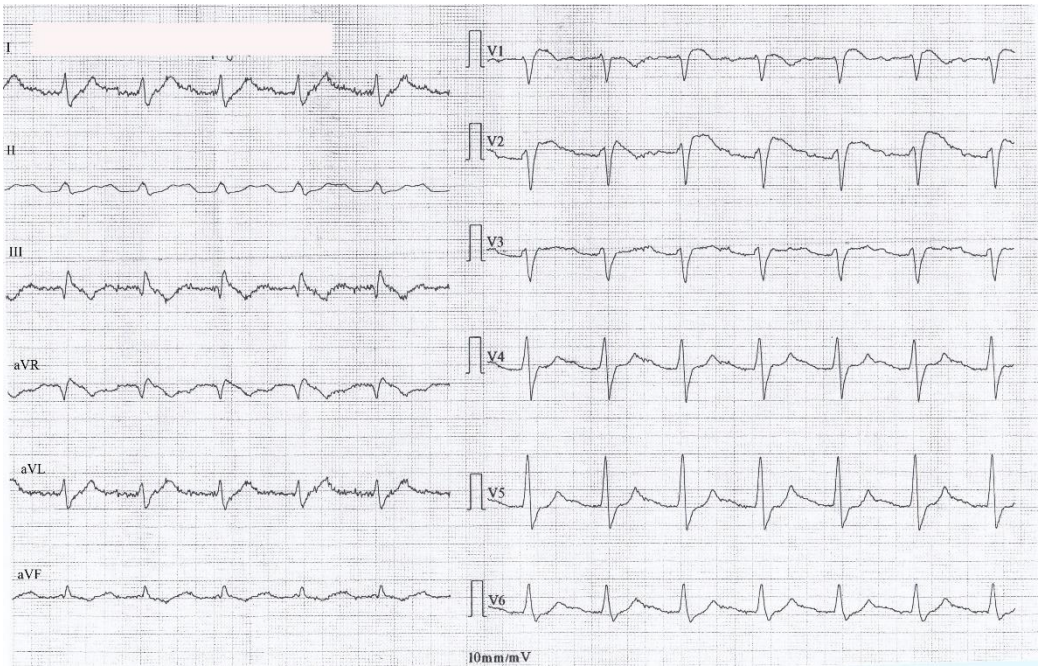
Table II.1. The evolution during ED admission and therapy provided.

Time after Exposure	Investigations and Therapy Administered	Patient Evolution
5 h after drug ingestion (ED admission)	Monitoring, blood samples drawn for hematological, biochemical, toxicological tests ECG recording IV line with saline solution 500 mL, sodium bicarbonate 8.4% 50 mL Activated charcoal 50 g orally Cardiac ultrasound	Symptoms: fatigue, headache Signs: GCS 12 BP 110/80 mmHg HR 71 bpm SaO2 95% room air
6 h after drug ingestion (First hour in ED)	Second ECG recording showing significant changes (Figure 2a) Additional sodium bicarbonate 8.4% 250 mL Sodium bicarbonate 8.4% 200 mL ECG recording showing wide QRS complex rhythm (Figure 2b)	GCS 13 BP 103/67 mmHg HR 67 bpm SaO2 97% (oxygen 2l nasal canula) Symptoms: dizziness, palpitation
7–8 h after drug ingestion (Second to third hour in ED)	IV administration of MgSO4 2 g over 20 min ECG recording showing VT (Figure 2c,d) A bolus of 1.5 mL/kg lipid emulsion (Intralipid®) pushed over 2–3 min, which was repeated, followed by 0.25 mL/kg/min infusion over the next hour ECG changes improved after first 20 min of LET (Figure 3a,b)	GCS 13 BP 95/65 mmHg HR variable 97–110 bpm SaO2 97% (oxygen 2l nasal canula) Symptoms: fatigue, palpitations
9 h after drug ingestion (Four hours after ED admission)	ECG changes restored to admission pattern LET completed Second dose of 25 g activated charcoal Admission for further monitoring and therapy in a medical ward	GCS 14 BP 108/78 mmHg SaO2 96% room air Symptoms: fatigue, anxiety

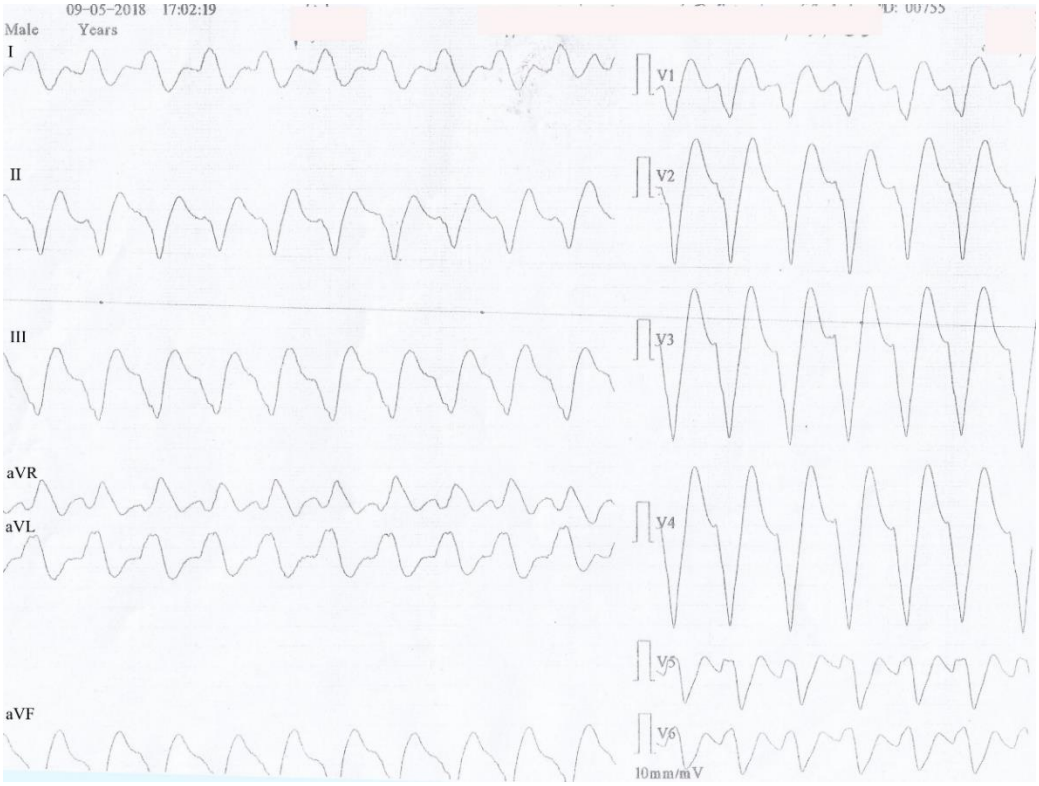
GCS, Glasgow Coma Scale score; VT, ventricular tachycardia: LET, lipid emulsion therapy.

One hour after admission, the ECG changed significantly and VT occurred later (Figure II.2). First, we administered MgSO4 2 g over 20 min, then a bolus of 1.5 mL/kg lipid emulsion

(Intralipid® 20% IV fat emulsion) was pushed over 2–3 min, which was repeated, followed by 0.25 mL/kg/min infusion over one hour.



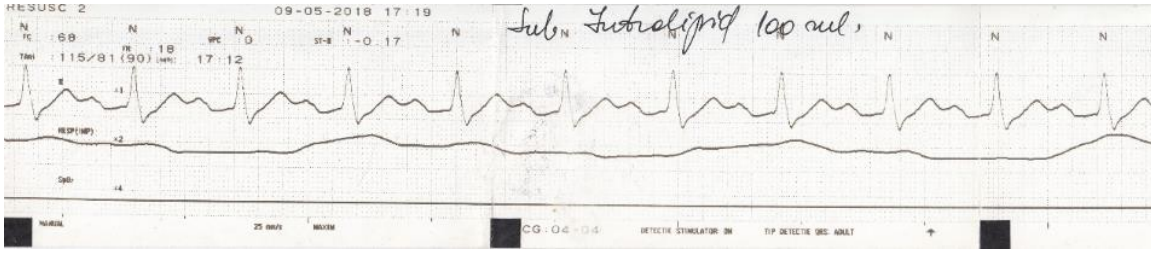
a. One hour after ED admission (6 h after drugs ingestion): sinus rhythm 67/min, prolonged PR 360 msec, wide QRS 200 msec, prolonged QTc 549 msec, negative T in DIII, aVF, with a coved ST segment elevation in V1-V2.



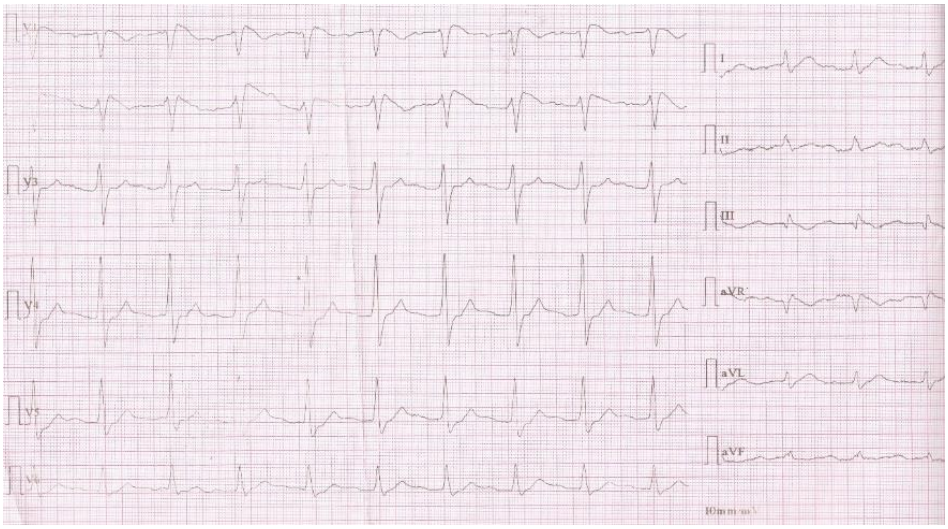
b. Two and a half hours after ED admission (7 and a half hours after drug ingestion): VT 110/min (wide QRS complex tachycardia, AV dissociation, negative concordance in precordial leads, R to nadir S 160 msec).

Figure II.2. Serial ECG recordings documented ventricular arrhythmia.

ECG changes showed significant improvement in 20 min after only 100 mL Intralipid® (Figure II.3).



a. Monitor recording during first 100 mL Intralipid® solution revealing reversal of ECG changes: sinus rhythm 68/min with distinct visible P waves, prolonged PR interval 320 msec, wide QRS complex 160 msec, QT interval 480 msec.



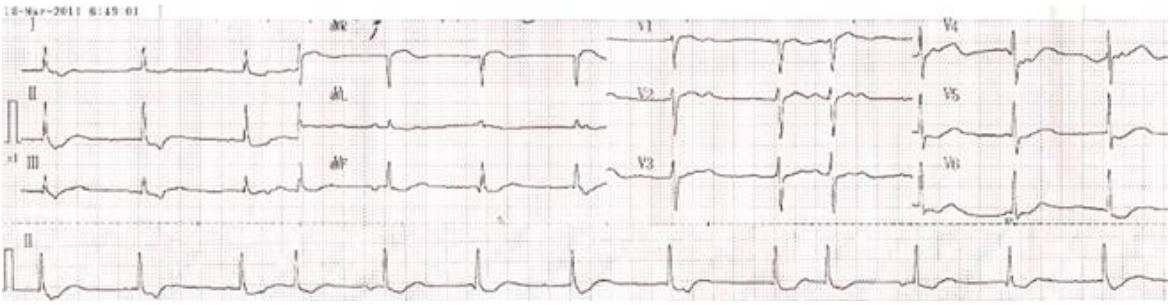
b. 12-lead ECG recorded after administration of the first 100 mL Intralipid®: sinus rhythm 71/min, first degree AV block (PR interval 320 msec), wide QRS complex RBBB-type 180 msec, disappearance of negative T waves in aVF, corrected QTc interval 479 msec.

Figure II.3. ECG recordings during LET.

During his ED stay, the patient remained hemodynamically stable. He was admitted to a medical ward, had no other complications, and was released home 48 h later. The ECG returned completely to normal baseline and the psychiatric medication was properly re-initiated. The toxicological results, which were not available during ED stay, showed in this patient a level of 4.8 mg/L amiodarone and 2.98 mg/L flecainide from the blood sample obtained upon ED admission (5 h after drug ingestion). These levels were extremely high compared with the usual therapeutic range, which is 1–2.5 mg/L for amiodarone and 0.2–1 mg/L for flecainide (Knollmann & Roden, 1996).

We also reported the second case of acute diltiazem overdose treated with LET that has survived. An 81-year-old woman, at the second suicide attempt, was brought to the ED by ambulance, with the suspicion of an overdose of cardiovascular medication from her own prescription. The patient was found lying unconscious on the floor in her apartment by her son around 11:00 am. The family mentioned that about 1 hour before they have communicated with the patient and she was in a good overall condition. Her medical history was relevant for hypertension and ischemic heart disease, for which was chronically treated with diltiazem and indapamide. Physical examination upon admission showed an unconscious old woman with a Glasgow Coma Scale score of 4, heart rate of 50 beats per minute, respiratory rate of 32 breaths per minute, blood pressure of 80/40 mm Hg. She had bronchial rales on both lungs and an oxygen saturation of 80%. She was admitted in the ICU and promptly received tracheal

intubation and mechanical ventilation. At the arrival time, the arterial blood gas revealed metabolic acidosis: pH 7.20, bicarbonate level of 12.6 mmol/L, base excess of 17 mmol/L, lactate level of 10.7 mmol/L, glucose of 366 mg/dL, urea of 41 mg/dL, and creatinine of 1.1 mg/dL. We did not measure the serum diltiazem concentration (not available in our hospital). Chest radiography showed bilateral diffuse infiltrates. Electrocardiogram showed sinus bradycardia. She was treated with 4 L of intravenous crystalloid solution and 4 g of calcium gluconate followed by an infusion of 1 mL/kg per minute. In the same time, an infusion with epinephrine was started in a dose of 1 μg/kg per minute. We also performed gastric lavage, and 50-g activated charcoal was administered on gastric tube. Approximately 4 hours from admission, despite aggressive fluid resuscitation associated with calcium and hyperglycemic euglycemia therapy, her condition remained critical. Electrocardiogram showed Mobitz II of 4/1 second-degree atrioventricular block, followed by atrio-ventricular dissociation (figure II.4).



ECG reveals atrio-ventricular dissociation, with escape junctional rhythm and some ventricular captures, and signs of ischemia in inferior and lateral leads.

Figure II.4. ECG changes in diltiazem poisoning.

We gave 100 mL of 20% Intralipid® followed by an infusion of 0.5 mL/kg per hour for 12 hours, leading to a favorable evolution. The systolic blood pressure increased at 120/70 mm Hg; heart rate was 72 beats per minute. The patient was stable hemodynamically and metabolic in the following 24 hours. She was alert and oriented and was extubated on the second day. She informed that she had taken 96 tablets of 60 mg diltiazem and 16 tablets of 1.5 mg SR indapamide at two hours before she was found irresponsive, on the day she was admitted. She was discharged after 4 days in a good state and without any neurologic deficits.

The flowchart of the review is presented in Figure II.5. For each article, we analyzed relevant demographic and clinical data from the case, hemodynamic variability due to the drug, then the drug dose and timing along with timed vital signs. Next, a thorough analysis of each ECG pattern, investigations, differential diagnosis, management, and outcome was performed. We also analyzed therapeutic approaches and the department where the treatment was conducted.

Despite the increasing awareness of LET therapy, more clinical studies and research are needed to explain better its mechanism of action, other appropriate indications, optimal dosing, and associated complications. LET therapy is relevant to physicians, advanced care providers, nursing teams, pharmacists, and ancillary staff across the interprofessional healthcare team, especially in anesthesiology, emergency medicine, and critical care. The decision to use LET requires strong clinical judgment on the part of the ordering clinician, especially in the setting of ED, when faced with a dramatic ECG change in subjects overdosed with antiarrhythmic drugs.

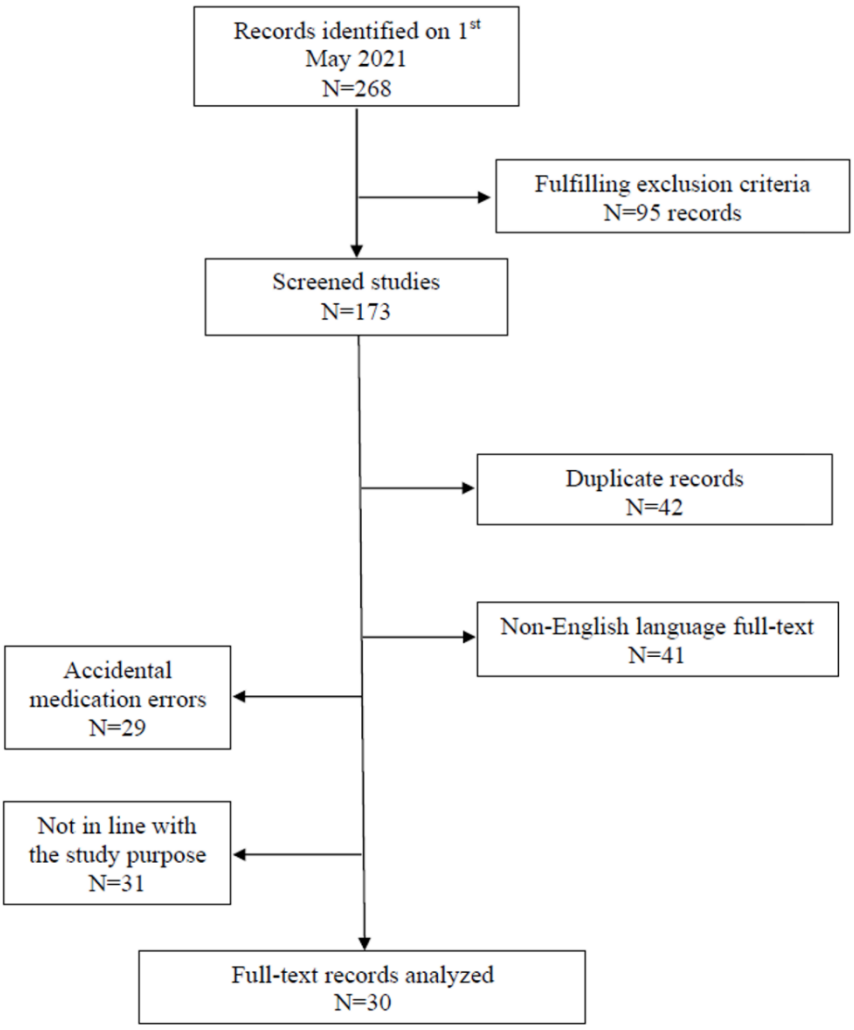


Figure II.5. Flowchart illustrating studies in included and excluded in this literature review.

A summary of the details of the included papers in the review is reported in Table II.2.

Table II.2. Characteristics and main findings of eligible studies.

Author(s), Year	Demographic/ Time/ Intent	Medication/Dose/ Serum Level * /Co-ingestions	ECG Patterns	Therapy/ Setting	Outcome
Bonati et al., 1983	W, 20-y/ 12 h/ Intentional	A/8000 mg/ 1.1 mg/L /no	Bradycardia, prolonged QTc	Supportive/ Medical department	Survival
Winkelmann et al., 1987	W, 28-y/ 2 h/ Intentional	F/3800 mg/ 3.7 mg/L /diazepam, loperamide, ethanol	Monomorphic VT, polymorphic VT	ACLS, Na bicarbonate, Na chloride, physostigmine salicylate, GL, AC/ ICU	Survival
Yasui et al., 1997	W, 20-y/ 90 min/ Intentional	F/NR/ 5.45 mg/L /ethanol	Idioventricular rhythm 40/min	Hypertonic saline, pacing, CBS/ ED, ICU	Death
Goldman et al., 1997	M, 16-y/ 30 min/ Intentional	F/4000 mg/ NR /no	VT, irregular WCT, prolonged QTc	Cardioversion, Na bicarbonate, lidocaine, GL, AC/ ED, ICU	Survival

Hanley et al., 1998	W,15-y/ 1 h/ Intentional	F/9000 mg/ 5 mg/L /no	Wide QRS irregular bradycardia, VT, prolonged QTc, AV block	Atropine, GL, AC, adrenaline, ECV, lidocaine, isoprenaline, pacing/ ICU	Survival
Lovecchio et al., 1998	1. W, 38-y/ 40 min/ Intentional 2. M, 61-y/ 8 h/ Intentional	1. F/1000 mg/ 2.18 mg/L /caffeine 2. F/3500 mg/ 3 mg/L /ig, losartan, ranitidine	1. Irregular rhythm, wide QRS 2. AF 105/min, wide QRS	1. GL, AC, supportive, Na bicarbonate/ED, ICU 2. repeated boluses of Na bicarbonate/ NR	1.Survival 2.Survival
Brazil et al., 1998	M, 36-y/ 6 h/ Intentional	F/10,000 mg/ 3.32 mg/L /no	Wide QRS, VT, PEA cardiac arrest	Na bicarbonate, ACLS/ ED, CCU	Death
Corkeron et al., 1999	W,20-y/ 15 min/ Intentional	F/4000 mg/ 4.25 mg/L /paracetamol	Irregular wide complex rhythm, PEA	CPR, Na bicarbonate, AC, adrenaline, pacing, CBP, CVVH/ ED, ICU	Survival
Auzinger et al., 2001	M, 30-y/ 1 h/ Intentional	F/6000 mg/ 20.52 mg/L /NR	Wide complex bradycardia	CPR, Na bicarbonate, pacing, ECMO/ ED, ICU	Survival
Siegers & Board, 2002	W,45-y/ NR/ Intentional	F/2000 mg/ 0.85 mg/L /ethanol	Bradycardia, pulseless VT, VF	CPR, ACLS, GL, AC, Na bicarbonate, amiodarone/ ED, ICU	Survival
Hudson et al., 2004	M, 70-y/ NR/ Accidental	F/1500 mg/ 2.96 mg/L /no	Wide complex rhythm, Brugada-type STE	Repeated Na bicarbonate boluses, supportive/ Medical unit	Survival
Timperley et al., 2005	W,47-y/ NR/ Accidental	F/NR/ 2.34 mg/L /amitriptyline, losartan, amlodipine	AF, wide QRS, sine wave appearance	Alteplase (for presumptive ACS), dobutamine, adrenaline, IABP/ ED, CTU	Survival
Devin et al., 2007	W, 34-y/ 90 min/ Intentional	F/4500 mg/ 3.6 mg/L /no	Irregular wide complex rhythm	Supportive, sodium bicarbonate/ ED, ICU	Survival
Rognoni et al., 2009	W, 57-y/ NR/ Intentional	F/1800 mg/ 1.94 mg/L /no	RBBB, wide QRS, prolonged QTc	Supportive, AC, MgSO4, Na bicarbonate/ ED, ICU	Survival
Vivien et al., 2010	W,40-y/ 10 h/ Intentional	F/12,000 mg/ 34 mg/L /betaxolol	Wide QRS bradycardia, Brugada-type, asystole	CPR, Na bicarbonate, epinephrine, dobutamine, ECMO/ ED, ICU	Death
Stellpflug et al., 2011	W, 30-y/ 6 h/ Intentional	A/NR/ 2.7 mg/L /diltiazem, metoprolol	Paced rhythm, no change in interval/ segment length	Supportive, calcium, HDI, LET/ ED, ICU	Survival
Ellsworth et al., 2013	M, 51-y/ 90 min/ Intentional	F/2500 mg/ 1.8 mg/L /no	Bradycardia, 1st degree AV block, wide QRS, prolonged QTc	AC, Na bicarbonate, Atropine, MgSO4, LET/ ED, ICU	Survival
Sivalingam et al., 2013	W, 52-y/ NR/ Intentional	F/NR/ 4.13 mg/L /no	Profound bradycardia, wide QRS, PEA	Pacing, CPR, ACLS, AC, Na bicarbonate, LET, ECMO/ ED, ICU	Survival
Reynolds & Judge, 2015	W, 24-y/ NR/ Accidental	F/400 mg/ 11.085 mg/L /caffeine, levetiracetam	Wide QRS bradydysrhythmia, PEA cardiac arrest	Na bicarbonate, vasopressors, pacing, LET, ECMO/ ED, ICU	Survival
Mandawat et al. 2015	W, 33-y/ NR/ Intentional	F/1800 mg/ NR /no	Wide complex rhythm, VT, prolonged QTc, PEA	Na bicarbonate, LET, ACLS, ECMO/ ICU	Survival

Williamson et al., 2015	W, 18-y/ 45 min/ Intentional	F/1200 mg/ NR /no	Wide QRS bradycardia, WCT	Atropine, Na bicarbonate, dobutamine, epinephrine, MgSO4/ ED, medical ward	Survival
Mukhtar et al., 2015	W, 13-y/ 90 min/ NR	F/900 mg/ 2.699 mg/L /bisoprolol	1st degree AV block, RBBB, prolonged QTc, VT, TdP, Brugada-like syndrome, VF	Na bicarbonate, MgSO4, glucagon, CPR, LET, pacing/ ED, ICU	Survival
Jung et al., 2016	M, 20-y/ 1 h/ Intentional	F/5000 mg/ NR /no	Irregular wide QRS bradycardia, pulseless VT, prolonged QTc, TdP, VF	Supportive, dopamine, CPR, Na bicarbonate, MgSO4, lidocaine, GL, AC, amiodarone, ECV/ ED, ICU	Survival
Vu et al., 2016	M, 23-y/ NR/ Intentional	F/NR/ 2 mg/L /amphetamine	Wide complex rhythm, pulseless VT, VF	CPR, Na bicarbonate, pacing, ECMO/ ED, CCU	Survival
Mullins et al., 2017	1. M, 49-y/ NR/ Intentional 2. M, 69-y/ 70 min/ Intentional	1. F/2400 mg/ NR /no 2. F/1000 mg/ NR /clonazepam, ropinirole	1. Bradycardia, asystole, wide QRS 2. Wide complex irregular rhythm, prolonged QTc, wide QRS	1.Atropine, glucagon, CPR, dopamine, Na bicarbonate, LET/ ED 2. Na bicarbonate, ALS, LET/ ED, CCU	1.Survival 2.Survival
Apfelbaum et al. 2018	W, 86-y/ NR/ Accidental	F/NR/ 1.39 mg/L /no	Wide complex rhythm, pacemaker spikes	Supportive, Amiodarone, Na bicarbonate, reprograming pacemaker/ ED, ICU	Survival
Bodziock et al., 2018	M, 48-y/ NR/ Intentional	F/NR/ 3.03 mg/L /no	Irregular sinusoidal waveforms, prolonged QTc, wide QRS, ST-depressions, T-wave inversions	Pacing, epinephrine, supportive, metoprolol/ ED, Cardiology service	Survival
Heldens et al., 2019	W, 68-y/ NR/ Accidental	F/NR/ 2.44 mg/L /no	Extreme broad QRS complexes, loss of pacemaker capture	Na bicarbonate, CVVH, LET/ ED, CCU	Survival
Gaylor et al., 2019	W, 30-y/ NR/ Intentional	F/1500 mg/ 2.01 mg/L /ondansetron	Cardiac arrest, wide complex arrhythmia, prolonged QTc	CPR, Mg, K, epinephrine, defibrillation, LET/ ED, CCU	Death
Venkata-raman, 2020	M, 70-y/ 4 h/ Accidental	F/900 mg/ NR /no	WCT, RBBB, anterior ST segment elevation	Na bicarbonate/ ED	Survival

*, serum level reported for each case was transformed in mg/L; W, woman; A, amiodarone; F, flecainide; VT, ventricular tachycardia; ACLS, advanced cardiac life support measures; GL, gastric lavage; AC, activated charcoal; ICU, intensive care unit; ED, Emergency Department; CBS, peripheral cardiopulmonary bypass support; AV, atrioventricular; ECV, electrical cardioversion; M, male; AF, atrial fibrillation; NR, not reported; WCT, wide complex tachycardia; PEA, pulseless electrical activity; CCU, coronary care unit; CVVH, continuous veno-venous hemodiafiltration; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; VF, ventricular fibrillation; STE, ST segment elevation; ACS, acute coronary syndrome; IABP, intra-aortic balloon pump; CTU, cardio-thoracic unit; HDI, high-dose-insulin therapy; LET, lipid emulsion therapy; RBBB, right bundle branch block; TdP, torsade de pointes; ALS, advanced life support.

Discussion

There are reports of accidental overdose in patients treated chronically with flecainide, especially in elders with hepatic or renal comorbidities, that were resolved in the ICU (Apfelbaum et al., 2018; Heldens et al., 2019; Donthi et al., 2020). There are also reports of flecainide-induced therapy resistant ventricular fibrillation followed by cardiac arrest, successfully treated with cardiopulmonary resuscitation and advanced life support, where amiodarone was used as part of the protocol (Siegers & Board, 2002; Jung et al., 2016;

Apfelbaum et al., 2018). From the studies analyzed, only in one case of accidental flecainide overdose was the patient managed successfully in the ED with Na bicarbonate (Venkataraman, 2021). All the other reports involved patients in need of exceptional measures, started in the ED and continued in ICU/CCU (Table II.2). In our review, we found two reports of deceased patients, both after ingestion of 10–12 g flecainide. The patients had an unfavorable outcome despite the administration of sodium bicarbonate (250 mL) and ACLS therapies, including ECMO - Table II.2 (Brazil et al., 1998; Vivien et al., 2010). Another patient, with a moderate dose of flecainide ingested in association with other drugs, also had an unfavorable evolution after ED and CCU therapy, which included CPR, administration of MgSO4, electrolyte correction, LET and defibrillation (Gaylor et al., 2021).

Antiarrhythmic drugs' toxicity can be classified based either on the clinical features, or on ECG changes. Flecainide's toxicity is rare but potentially fatal; at higher doses, flecainide toxicity can result in hemodynamic collapse, with a mortality rate of up to 22.5% (Koppel et al., 1990). Flecainide overdose determines nonspecific symptoms (nausea, vomiting, headache), seizures, bradycardia, QRS widening and ventricular arrhythmias (Lewin, 2002; Benowitz, 2012; Vu et al., 2016; Cheung & Man, 2002). Flecainide is a lipophilic drug that acts by strongly blocking the sodium channels, delaying their reactivation without impeding repolarization. Flecainide binds and opens sodium channels in a dose-dependent manner. In patients without structural heart disease, flecainide slows the conduction and favors reentry, creating areas of functional block, thus producing reentry arrhythmias. Among the class Ic antiarrhythmics, flecainide is the most difficult to detach from the sodium channels, delaying their reactivation (Banavalikar et al., 2018; Benowitz, 2012). The plasmatic peak is 3–4 h after flecainide ingestion. After absorption, 70% of the dose ingested is metabolized in the liver, while 30% is eliminated unchanged by the kidney. In patients with renal impairment, the total clearance of this drug might fall by approximately 40% (Subedi et al., 2018). The elimination time is dose-dependent, and is increased by urine alkalinization (Stellpflug et al., 2011; Mandawat et al., 2015).

Amiodarone inhibits several cytochrome P450 pathways, thus increasing serum concentrations of drugs such as statins, CCBs, tacrolimus, quinidine, fentanyl and flecainide. Plasma concentrations >2.5 mg/L have been associated with increased risk of toxicity (Van Erven & Schalij, 2010). Amiodarone is a class III antiarrhythmic with all the properties of the four Vaughn-Williams antiarrhythmic classes. After oral administration, the maximal plasmatic concentration is reached 3–7 h later (Benowitz, 2012; Van Erven & Schalij, 2010). Amiodarone affects bioavailability, binding with plasmatic proteins, metabolism by liver cytochromes and kidney elimination of co-administered antiarrhythmics. Thus, amiodarone significantly increases the plasma level of flecainide, leading to severe cardiotoxicity. Amiodarone is likely to cause polymorphic ventricular dysrhythmias and the effect is potentiated by hypokalemia or hyperglycemia (Krikler et al., 1983; Antonelli et al., 2005; Psirropoulos et al., 2001).

Large doses of sodium bicarbonate should be administered in flecainide overdose to counteract cardiotoxicity by plasma alkalinization, which decreases the free concentration of the drug, promotes drug dissociation from the sodium channels and increases extracellular concentration of sodium ions that displace the drug from the receptor sites (Banavalikar et al., 2018; Vu et al., 2016; Viland et al., 2019). The dose of the hypertonic sodium bicarbonate is 1 mEq/kg bolus (range, 0.55–3.0 mEq/kg) followed by infusion of 15 to 20 mEq/h, maintaining a target pH of 7.50 to 7.60 (Banavalikar et al., 2018).

LET is an adjunctive measure, which will sequestrate both flecainide and amiodarone, decreasing the drug available to block sodium channels (Vu et al., 2016; Viland et al., 2019). The mechanism of action of LET is unclear; however, it is postulated that it follows the

mechanisms of the "lipid-sink" theory whereby LET acts to sequester lipophilic drugs, such as flecainide, thereby reducing toxic activity on cardiac myocytes (Fettiplace et al., 2013). The administration of LET compartmentalizes the offending drug into a lipid phase and away from the target receptors. The drugs with a high lipid solubility favor the lipid partition and leave the serum, thus lower serum concentrations facilitate the removal of the offending agent from tissues by the generation of a concentration gradient (Fettiplace et al., 2015; Cao et al., 2015). The second mechanism suggests that LET exerts a positive inotropic effect with more efficient metabolization of fatty acids (Ellsworth et al., 2013). To our knowledge, ten cases have been published in the literature regarding the use of LET as part of a complex therapeutic protocol initiated in the ED, continued in ICU/CCU, for severe cardiotoxicity in flecainide overdose. LET was also used in one case of mixed poisoning including amiodarone, betablockers and CCBs. In reviewed cases, LET was associated (in addition to treatment with high doses of sodium bicarbonate) with ACLS measures, CPR, pacing, CVVH and ECMO (Reynolds & Judge, 2015; Mandawat et al., 2015; Sivalingam et al., 2013; Mukhtar et al., 2015; Mullins et al., 2017; Heldens et al., 2019; Gaylor et al., 2021). In a single case, in which the patient arrived at the ED 90 minutes after self-poisoning with a lower flecainide dose as compared with our patient, with a serum level of flecainide slightly over the therapeutic range, LET was involved as part of a pharmacological protocol that included atropine, MgSO4, Na bicarbonate for bradycardia, AV block and QTc prolongation. However, this case needed ICU surveillance (Ellsworth et al., 2013).

To our knowledge, ours was the first report of a suicide attempt after intentional ingestion of large doses of amiodarone and flecainide with severe cardiotoxicity and a favorable evolution after LET in the ED. Particular to this case was that it was recorded when, in our country, flecainide was not authorized by the National Agency for Medicines and Medical Devices. The use of LET immediately after occurrence of ventricular arrhythmias led to a significant improvement in QRS and QTc duration and the restoration of sinus rhythm, within 20 min, in the ED. While the evidence based informations for the LET use in acute drug intoxication is evolving, the present evidence and recommendation supports the use of LET in lipophilic cardiotoxin intoxication when there is an immediate threat to life, and other therapies have proven ineffective (Cave & Harvey, 2014; Stellpflug et al., 2016).

Patients who do not respond to drug therapy could benefit from cardiac pacing, ECMO, or mechanical circulatory support (Vu et al., 2016; Newson et al., 2020). ECMO is a temporizing measure to allow for cardiac recovery and drug elimination and should be reserved for refractory hemodynamic compromise (Valentino et al., 2017). Extra-corporeal life support (ECLS) provides respiratory support and also crucially maintains cardiac output, preventing end-organ damage and restoring vital organ perfusion, thereby enabling renal drug elimination, hepatic drug metabolism and drug redistribution. The length of the ECLS support may be determined by serum flecainide level and cardiac stability (Sivalingam et al., 2013).

The first step in the management of a mixed antiarrhythmic overdose should be recording an ECG to identify QRS widening, QTc prolongation, or atrio-ventricular blocks. The second step should be ABG determination and decontamination measures. Then, pharmacological therapies that proved to be beneficial, such as hypertonic sodium bicarbonate or LET, should be initiated early in the ED, when the first signs of cardiotoxicity occur. We reported the first case of intentional amiodarone and flecainide poisoning, drugs that interact, both leading to life-threatening cardiotoxicity. The patient was admitted to the ED 5 h after drug ingestion and initially had a nonspecific clinical picture. ECG signs of cardiotoxicity occurred 6 h after ingestion, although immediate measures for decontamination and hypertonic sodium bicarbonate were initiated. Alkalinization with a pH over 7.5 and increased extracellular sodium contribute to flecainide dislocation from cardiomyocytes and decrease

serum free flecainide level (Viland et al., 2019). LET was given after failure of other therapies, prior to cardiovascular collapse, as the VT occurred. ECG changes in our patient were improved within 20 min of LET. The patient remained hemodynamically stable with an uneventful evolution during the next 48 h of hospitalization.

In CCBs overdoses, the therapeutic measures must be aggressive and initiated as soon as possible. The first-line antidote treatment is calcium and should be administered initially intravenous in bolus and then in infusion. It is recommended to use calcium gluconate intravenous initial dose of 3 to 5 ampoules, 10% solution, followed by an infusion of 1 mL/kg per hour (Sheperd, 2006; Salhanick & Shannon, 2003). The second line of antidote treatment is represented by glucagon, which stimulates the adenylate cyclases at cellular level, short-circuiting in this way the calcium and the β receptors of the myocardium and determining a positive inotropic and chronotropic effect. The initial recommended glucagon doses is 2 to 10 mg administered intravenous followed by an infusion of 0.05 to 0.1mg/kg per hour (Olson et al., 2005; Tintinalli et al., 2011; Gunja & Graudins, 2011). A third line of therapy used, so-called metabolic treatment or HIE therapy, is represented by administration of insulin in association with hypertonic glucose. Insulin has the role of a positive inotropic agent, helping the heart to use more efficiently the carbohydrates, which will favorably influence the cardio-depressive syndrome. These patients tolerate high doses of insulin as a consequence of insulin resistance and hyperglycemia produced by this poisoning. Usually, one would start with an intravenous bolus of 1 IU/kg followed by an infusion of 0.5 IU/kg per hour in association with a bolus of 25 g of glucose followed by an infusion of 0.5 g/kg per hour (Marques et al., 2003; Tintinalli et al., 2011; Montiel et al., 2011). Another metabolic therapy recommended for toxic lipophilic agents is represented by LET administration to reestablish the physiologic and metabolic integrity of myocardium by increasing the transport of fatty acids. The administration protocol implies an initial intravenous dose of 1.5 mL/kg in 1 minute followed by an infusion of 0.25 mL/kg per minute (De Witt & Waksman, 2004; Cave et al., 2011; Hoffman, 2010; Rothschild et al., 2010; Liang et al., 2011; Young et al., 2009). This case was presented because, to the extent of our knowledge, it is the second case of acute diltiazem overdose treated with LET that has survived.

The LET was initially designed to treat cardiotoxicity induced by intravascular injection or local anesthetic overdose. The published cases with intravenous lipid emulsion for treating cardiotoxicity are few in the scientific literature, only 42 cases, 19 of which had local anesthetics overdoses and 23 had non-anesthetic cardiotoxic medication such as tricyclic antidepressants, CCBs, and beta-blockers (Montiel et al., 2011; Cave et al., 2011; Rothschild et al., 2010; Liang et al., 2011; Young et al., 2009).

CCBs cause cardio-depressive syndrome through blockage of calcium channels that are found in myocardium and smooth muscle cells (Gunja & Graudins, 2011; Salhanick & Shannon, 2003; De Witt & Waksman, 2004). Diltiazem depresses sinoatrial and atrioventricular nodal conduction, decrease myocardial contractility, and decrease peripheral vascular resistance. In myocardial tissue, this results in negative inotropy, chronotropy, and dromotropy. In vascular tissue, this results in arterial smooth muscle relaxation. CCBs are also considered metabolic poisons (Gunja & Graudins, 2011; Salhanick & Shannon, 2003). The heart is dependent on free fatty acids for energy. In CCB overdose, the heart becomes more dependent on carbohydrates for energy, and insulin release from the pancreas is blocked. As a result, the ability of the heart to use the preferred energy substrate efficiently is exacerbated (Gunja & Graudins, 2011; Salhanick & Shannon, 2003; Marques et al., 2003). This determines appearance of hyperglycemia and lactic acidosis, further depressing the myocardial contractility (Salhanick & Shannon, 2003; Marques et al., 2003; De Witt & Waksman, 2004).

The mechanism for LET that has been initially termed lipid rescue has not yet been fully elucidated (Hoffman, 2010; Rothschild et al., 2010; Liang et al., 2011). However, subsequent research has moved from the "lipid sink" theory to the combined effects of multiple scavenging and non-scavenging mechanisms (Sepulveda & Pak, 2021). Myocardial extraction of free fatty acids is decreased in CCB overdose despite maintained plasma levels (Hoffman, 2010). The beneficial effect LET is enhancement of myocardial fatty acids transport, which restores the physiologic and metabolic integrity of the myocardium (Hoffman, 2010). Intravenous lipid emulsion therapy determines an expanded intravascular lipid phase named "lipid sink". The lipophilic drugs will repartition into this space moving away from affected organs, thereby reducing the amount of drug available to exert its toxic effects. This mechanism of an altered volume of distribution as a result of binding in a "nontoxic space" is similar to the use of digoxin specific antibody fragments or multiple doses of activated charcoal (Hoffman, 2010; Rothschild et al., 2010). A static lipid phase reservoir would become rapidly filled before removing enough drug from the plasma circulation to recover toxicity. Instead, ongoing research better supports ILE as a dynamic "lipid shuttle" or "lipid subway" (Fettiplace & Weinberg, 2018)

Our report demonstrates that LET can be effective in CCB overdose. The optimal dose, timing, and duration of therapy remain unclear. In our case, we based on previous case reports fat emulsion therapy protocols (Montiel et al., 2011; Cave et al., 2011; Liang et al., 2011). Our patient has not developed adverse effects of intravenous lipid emulsion such as acute lung injury or hyperamylasemia. For all cases with lipophilic drug overdoses and hemodynamic instability, when standard resuscitation protocols are unsuccessful, clinicians can consider administration of intravenous lipid emulsion (Tintinalli et al., 2011; Liang et al., 2011). This method of treatment is currently considered one of the standard treatments for CCB and beta-blocker overdoses, being used as a monotherapy or in association with HIE therapy. LET is now recommended in advanced cardiac life support guidelines for cardiac arrest secondary to lipophilic agents (Cave et al., 2011; Young et al., 2009; Rothschild et al., 2010).

Conclusions

LET might be considered in cardio-depressive syndromes resulting from CCB overdose if this does not respond to standard resuscitation measures. With these reports and the data reported in the literature, we wanted to point out that: (a) emergency physicians need to proceed to close cardiac monitoring of the patients with CCB or mixed antiarrhythmics poisoning; (b) administration of life-saving therapies, such as hypertonic sodium bicarbonate and LET after first cardiotoxicity signs, is feasible in the ED and should help to avoid the need for exceptional measures in the ICU. Since antiarrhythmics are widely used in clinical practice, further research on pharmacological therapies and antidotes is crucial for taking an important preventive action.

II.2. The role of Molecular Adsorbent Recirculating System (MARS) in the management of patients poisoned with non-edible mushrooms.

This direction of research is reflected in the following published articles:

1. Sorodoc, L; **Lionte, C**; Sorodoc, V; Petris, O; Jaba, I. Is MARS system enough for A.phalloides-induced liver failure treatment? *Hum & Exp Toxicol* 2010; 29(10): 823-832. (**IF 1.211**)
2. Successful treatment of an adult with Amanita phalloides-induced fulminant liver failure with molecular adsorbent recirculating system (MARS). **Lionte C,** Sorodoc L, Simionescu V. *Rom J Gastroenterol*. 2005; 14(3): 267-71. (ISSN:1221-4167) **PMID: 16200238**

Background

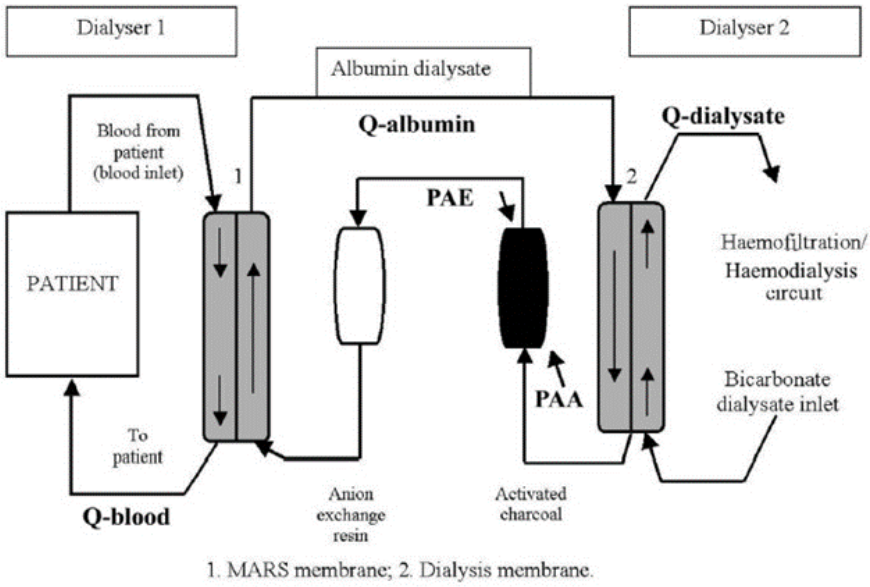
Fulminant liver failure (FLF) is defined as sudden onset of severe liver failure (LF) associated with jaundice and altered mental status known as hepatic encephalopathy (HE) in the absence of preexisting liver disease (Tan, 2004). FLF, the most severe form of LF is produced, among other causes, by toxins, such as those from the Amanita phalloides (Sherlock & Dooley, 1993; Tan, 2004). As reported in literature, the mortality rates for patients with FLF without liver transplantation (LT) approaches 80%, despite advances in intensive care management (Novelli et al., 2002; Covic et al., 2003; Lionte et al., 2004). LF associated with excretory insufficiency and jaundice results in an endogenous accumulation of toxins (involved in the impairment of cardiovascular, kidney, cerebral function) and damage to the liver itself by inducing hepatocellular apoptosis and necrosis, thus creating a vicious cycle of the disease (Stange et al., 2000). Treatment is directed to early recognition of the complications and general supportive measures, but the only proven therapy for patients unlikely to recover remains LT (Gill & Sterling, 2001).

More than 90% of all fatal cases of mushroom poisoning are secondary to A. phalloides (Donnelly & Wax, 2005). Its rapid evolution towards FLF makes poisoning with A. phalloides a medical emergency. Due to the development of acute tubular necrosis, and subsequent renal failure worsening LF, as well as rising ammonia levels, hepato-renal syndrome, hepatic coma and convulsions occur, followed by respiratory failure, hemorrhage, and death by days 6–16 (Donnelly & Wax, 2005; Lionte et al., 2002). Once a diagnosis of A. phalloides poisoning has been established, the patient's care is mainly supportive, as no specific antidote exists for its toxins. Controversy still remains whether hemoperfusion, hemodialysis, or both, are effective in averting the deleterious effects of amatoxins. Several studies have suggested that early hemoperfusion (<24 hours after exposure) over a charcoal filter should be considered if patients fulfill the criteria of time from ingestion, biochemical evidence of toxicity, ingestion of a potentially lethal dose and elevation of serum enzymes (Aji et al., 1995). Orthotopic LT should be considered in patients who progress to HE with significant and worsening derangement of both clotting factors and liver enzymes (Scheurlen et al., 1994).

There is no evidence from randomized trials to support a standard intervention or therapy for FLF in A. phalloides poisoning. There were reports of using Molecular Absorbent Recirculating System (MARS) in the treatment of FLF secondary to mushroom poisoning, in children and in adults (Lionte et al., 2002; Rubik et al., 2004; Wu & Wang, 2004; Catalina et al., 2003; Shi et al., 2002; Lionte et al., 2005; Hydzik et al., 2005; Sein Anand et al., 2005; Sein Anand et al., 2007). MARS therapy has been shown efficient in removing bilirubin, bile acids, tryptophan, aromatic amino acids, middle and short chain fatty acids, inflammation mediators, also decreasing the HE's grade, improving the liver synthesis function and most importantly, increasing survival (Stange & Mitzner, 1996; Lionte et al., 2005).

The molecular absorbent recirculation system (MARS) is a two-circuit system, which allows albumin-bound toxins to be removed (Lee et al., 2011). The MARS system consists of a 20% albumin closed-loop circuit, with two areas of depuration (Figure II.6). In one area, the toxin-free 'albumin dialysate' is in contact with patient's blood through an asymmetric permeable polysulfone membrane – the MARS™ membrane (pre-perfused with albumin 20%, to saturation). Albumin-bound substances are transferred from patient's serum albumin to the unoccupied ligand binding sites of the system's albumin. In the second area, the 'albumin dialysate' is in contact with a standard bicarbonate dialysate through a high-flux membrane, which permits the elimination of water-soluble substances. The albumin toxin charged solution is continuously regenerated by deligandization obtained by passage on charcoal and ion-exchange columns. This principle allows the replacement of the liver's detoxification function, which is life threatening while absent in liver failure (Stange, 2011).

The indications of this enhanced elimination method in clinical toxicology are: acute toxic liver failure induced by wild mushrooms, such as Amanita Phalloides, acetaminophen etc. (Lionte et al., 2005; Sorodoc et al., 2010; Wittebole & Hantson, 2011), acute poisoning with substances binding of plasmatic proteins (Sorodoc et al., 2009; Wittebole & Hantson, 2011). The relative contraindications of the method are a progressive coagulopathy indicative of disseminated intravascular coagulation (DIC), uncontrolled sepsis or bleeding (Lionte et al., 2005; Wittebole & Hantson, 2011).



Albumin-bound toxins from the patient's blood pass on to the albumin in the dialysate, which is then cleansed sequentially by a haemodialysis/haemofiltration module (removing water soluble substances) and adsorber columns containing activated charcoal and anion exchange resin (removing most of the albumin-bound substances). The dialysate is thus regenerated, and once more capable of taking up more toxins from the blood. AP = albumin pump; BP = blood pump (reproduced from Sorodoc, Lionte et al., 2010).

Figure II.6. Schematic diagram of the MARS circuit.

Aim of the research

The aims of the current study were to evaluate the feasibility, safety and efficacy of nine MARS sessions (three per patient), as well as impact on survival, comparative with optimal intensive care (OIC) in six consecutive adults poisoned with A. phalloides and secondary LF, in the setting of an ICU in Romania. We describe the first Romanian experience with MARS therapy in A. phalloides-induced FLF in adult patients, considering that LT is not accessible in Romania for this etiology of FLF.

Methods

We studied retrospectively six consecutive patients accidentally poisoned with A. phalloides, who developed FLF, between September and November 2007. We analyzed this period because in 2007, we recorded 7 cases of A. phalloides poisoning (of which 6 were consecutive cases, in the fall of 2007), compared with 2 cases in 2008, and one case in 2009, and because MARS procedure was introduced in October 2007 for the first time in our ICU. Data were collected from hospital medical records. Inclusion criteria were FLF supported by clinical symptoms and biochemical parameters, with progressive clinical deterioration despite OIC over 72–96 hours, with increasing jaundice (bilirubin >7 mg/dL), and either HE (≥ Grade 2) or renal failure or both, and A. phalloides spores detected by mycological analysis in gastric content or stool. There was no statistically significant difference in clinical and biochemical

parameters between OIC group and MARS group (Tables 1 and 2). Exclusion criteria age was < 16 years old, more than 5 days from the moment of mushroom ingestion, or severe cardiorespiratory disease.

The following technical parameters were used for MARS sessions: flow rates (Q) as follows – Q-albumin =150 mL/min, Q-blood = 100–150 mL/min, Q-dialysate = 2,000 mL/hour; P_{AA} was between 100 and 225 mmHg (max = 400) and P_{AE} between 130- and 400-mm Hg (max = 500), as Figure 1 shows. MARS group consisted of three patients, each of them received three MARS 6-hour sessions (a total of nine MARS sessions). Clinical course, biochemical parameters and survival was compared to that of OIC group (3 cases), matched for ALT levels and HE grade, hospitalized before the introduction of MARS therapy in our ICU.

The patients were evaluated clinically and biochemically (including liver and renal function tests, hematological and coagulation profiles) both 15 min prior to and 24 hours after each MARS session. The Child-Turcotte Pugh (CTP) score, the Model for End-stage Liver Disease (MELD) score were calculated at the same time (Pugh, 1973; Kamath et al., 2001). These scoring systems are good predictors of the outcome in patients with liver disease and also in patients that are admitted with ALF (Jalan et al., 2003). The severity of HE was assessed using the West Haven criteria and Glasgow coma scale (Faulstich, 1979). Patients were mechanically ventilated if they became hypoxemic. Mean arterial pressure, electrocardiogram, heart rate and temperature were monitored continuously during treatment. Intravascular volume was maintained using crystalloids, colloids or red cells as appropriate to maintain central venous pressure between 8 and 10 cm H_2O. Dopamine was used to maintain mean arterial pressure above 55 mmHg where necessary. Blood glucose was maintained between 5 and 7 mmol/L. Results were expressed as the mean ± standard deviation. Statistical analysis was performed using Student's t-test and analysis of variance (ANOVA). $p < 0.05$ was taken as statistically significant.

Results

We studied six consecutive patients with A. phalloides poisoning and LF. Three patients (aged 38.83 ± 19.36 years) received OIC, because no hemofiltration/hemodialysis/charcoal hemoperfusion were available at the moment of their admission, and the other three (aged 37.13 ± 18.37 years) benefited from daily MARS (3 sessions each) and OIC. All three patients were jaundiced and encephalopathic at the time MARS was initiated (Table II.3). Their biochemical profiles are given in Table II.4.

Table II.3. Demographic, clinical parameters and outcome of patients included in study

Group	Case	Age (y.m)	BMI (kg/m^2)	Approx. amount of mushroom meal consumed (g)	Time to hospital admission (h) /time to first MARS session (h)	Encephalopathy grade (at MARS initiation)	SBP (mm Hg)/ HR (/min) at admission	Initial MELD score/GCS	ICU (d)/ Hospital (d)	Outcome/ after ingestion (d)
MARS	1	49.3	27.1	200	90 / 102	III	60 / 140	27 / 4	5 / 5	Death / 9
	2	16	24.7	150	16 / 89	II	100 / 110	17 / 7	5 / 8	Death / 8
	3	46.1	26.3	50	20 / 121	I	120 / 90	15 / 8	9 / 18	Survival / 90
OIC	4	30.3	31.2	200	24 / NA	NA	85/ 120	28 / 7	3 / 7	Death / 8
	5	61	33.1	250	36 / NA	NA	85 / 134	25 / 8	3 / 6	Death / 8
	6	25.2	27.3	150	48 / NA	NA	75 / 137	33 / 8	6 / 8	Death / 10
p value[a]		.94	.17	.18	.89/ NA	–	.62 / 0.47	.20/.26	.01/.44	–

BMI, body mass index; d, days; g, grams; h, hours; HR, heart rate; m, month; NA, not applicable (no MARS sessions performed); SBP, systolic blood pressure; y, year; GCS, Glasgow coma score. [a] Comparison between parameters in MARS group and OIC group.

Patient 3 of MARS group (Table II.3) survived and was discharged from the hospital with good liver function, not requiring further hospital admission, 3 months after inclusion into the study. This patient ingested the lowest amount of mushroom meal (50 g, with a ratio between

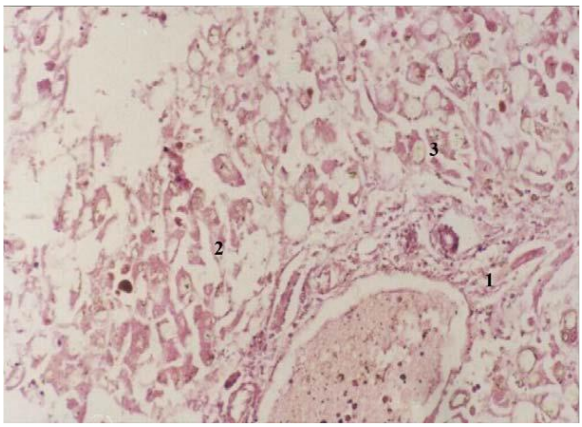
mushroom quantity and BMI of 1.9), as compared with the rest of the patients who ingested larger quantities (150 to 250 g, with higher ratio between quantity ingested and BMI, of 5.49 to 7.55). Even if this was not significantly statistic, we consider that the low amount of mushroom meal ingested contributed in some way to the survival of this patient.

Table II.4. Biochemical parameters of patients included in study.

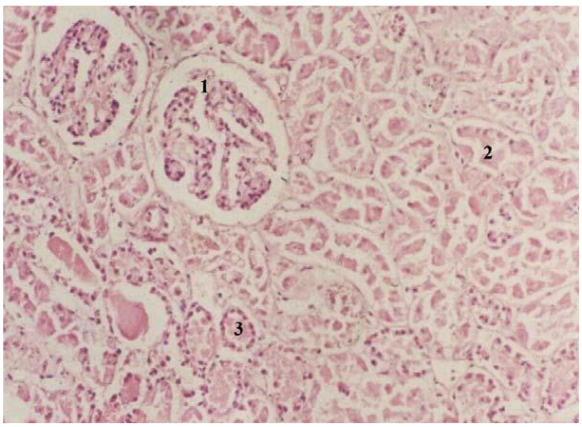
		Bilirubin (mg/dl)			ALT (IU/L)			Prothrombin time (s)			Ammonia (μmol/l)			Creatinine (mg/dl)		
Group	Case	b1/a1	b2/a2	b3/a3	b1/a1	b2/a2	b3/a3	b1/a1	b2/a2	b3/a3	b1/a1	b2/a2	b3/a3	b1/a1	b2/a2	b3/a3
MARS	1	6/5.2	7/4.6	6.9/5.9	16227/14320	12140/9360	3267/1860	101/56	65/55	70/63	193/54	91/73	150/108	3.8/2.6	1.9/.8	1.2/.8
	2	6.7/6.1	9.2/6.5	14.1/13.2	3397/3363	2388/1546	1541/863	140/125	129/105	108/95	298/68	416/330	270/219	4.2/1	2.9/1.8	.9/.6
	3	7.3/6.2	4.8/3.8	3.4/2.9	5514/4830	2188/1530	1656/969	74/35	29/21	22/15	167/56	66/46	39/27	5.9/ 3.6	6.6/3.8	1.7/.6
p Value[a]		.0015			.0045			.0044			.0110			.0043		
OIC	4	6	9.4	15.8	11836	5540	1746	104	64	69	91	150	108	1.6	1.8	2.4
	5	5.1	7.4	9.7	10508	8234	2468	62	104	319	87	169	306	2.8	3.9	5.1
	6	5.2	8.7	11.9	12916	8184	4276	86	127	205	69	135	203	5	6.24	6.4
p Value[b]		.36			.29			.20			.38			.43		

a1, parameter post MARS-1; a2, parameter post MARS-2; a3, parameter post MARS; 3b1, parameter pre-MARS-1; b2, parameter pre-MARS-2; b3, parameter pre-MARS-3. [a] Comparison between pre and post MARS parameters. [b] Comparison between pre-MARS parameters in MARS group and OIC group (the same interval from mushroom ingestion).

The other two patients died within 9, respectively 8 days after mushroom ingestion (mortality 66.7%). Patients poisoned with A. phalloides receiving only OIC had 100% mortality, within 8 days after mushroom ingestion. Pathology examination was performed to all deceased patients, and revealed typical liver and tubular renal lesions (Figure II.7) as well as the Amanita spores present.



a. Liver specimen: a fragment of portal-biliary space (1) with massive necrosis of hepatocytes (2), and cholestasis (biliary thrombi) (3). Hematoxylin and eosin stain x20.

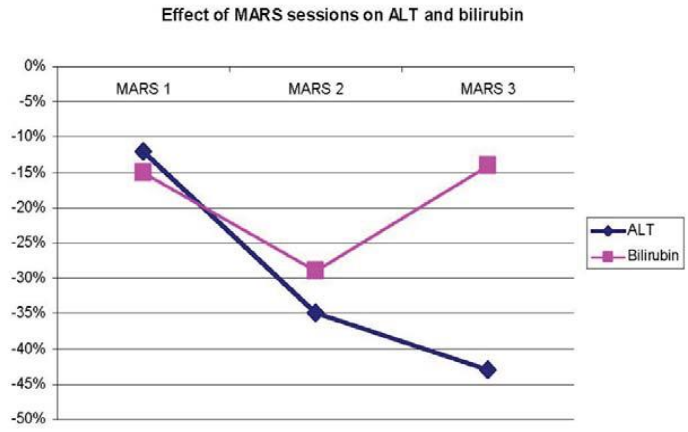


b. Kidney specimen: normal glomeruli (1), tubular proximal necrosis (2) seen in renal cortical. The contour of tubes is kept, but they have necrosis of the epithelium, with epithelial necrotic cells without nucleus detached in lumen. Rare images of tubes with epithelial regeneration (3). Hematoxylin and eosin stain x20.

Figure II.7. Pathology examination of liver and kidney after death in MARS group.

The MARS sessions had a similar immediate impact on biochemical parameters (Figure II.8): drop in ALT from pre-MARS levels of 12%, 35% and 43%, respectively, and in bilirubin of 15%, 29% and 14%, respectively ($p < 0.01$). ALT levels 24 hours following MARS-1 were 33% lower and continued to drop by a further 24%, 4% following MARS-2 and MARS-3, respectively. After 9 sessions, ALT decrease was statistically significant (p value 0.0045). Prothrombin time (PT) was also significantly improved with MARS sessions (p value 0.0044),

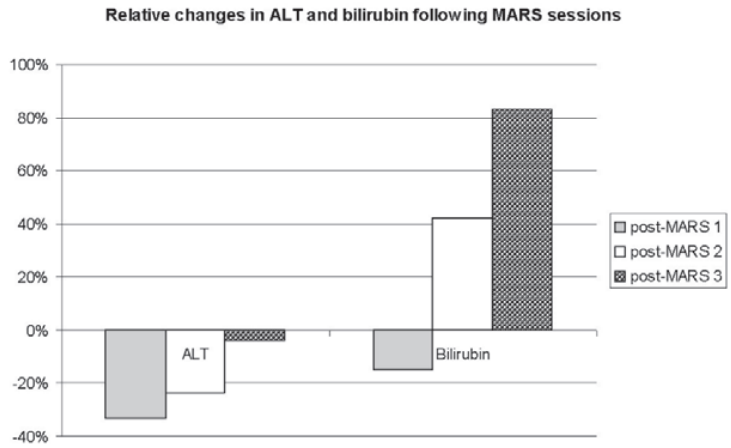
and normalized in patient 3, after MARS-2. Bilirubin levels were significantly decreased after MARS sessions (p value 0.0015).



p<0.01

Figure II.8. Immediate impact on biochemical parameters of MARS sessions.

However, 24 hours after receiving MARS-1 and MARS-2, there was a significant rebound in bilirubin levels (Figure II.9) in 2 cases, as follows: case 1 had a rebound of 34.6% and 50%, respectively, and case 2 had 50% and 116%, respectively, rebound of bilirubin level (p 0.048). All three patients were encephalopathic at the time MARS was initiated (Table II.3).



p<0.04

Figure II.9. Rebound in bilirubin levels 24 hours following MARS-1 and MARS-2.

Patient 3 regained consciousness after two sessions of MARS therapy. Pre-MARS, the CTP score was 6.7 ± 1.2, improved significantly to 4±1.6 following the three MARS sessions ($p < 0.05$), and further declined to 3.3±1.1 at time of discharge/death. Ammonia levels dropped from 219 ± 69 mg/dL pre-MARS to 59 ± 7 mg/dL post-MARS (p value 0.011) and further decreased to 44±16mg/dL in patient who survived, but increased to 105±33 mg/dL and 308±84 mg/dL, respectively, in the other two patients (p value 0.04) who had a bad outcome.

Markers on unfavorable outcome were delayed admission in hospital (4 days after mushroom ingestion in case 1), a lack of complete correction of PT, a continuous rebound and

increase in bilirubin levels, even after MARS-3 treatment, delay in MARS therapy initiation (cases 1 and 2) and a lack of improvement in HE scores post MARS-1.

The MARS procedure was completely uneventful and devoid of any incidents or complications. There was an increase in mean arterial pressure immediately after the MARS-1 (case 1) from 74.6 to 80 mm Hg, which was sustained through the treatment period (84 mm Hg at the end of therapy), but the changes were not statistically significant. There was neither decrease in hemoglobin or platelets, nor significant changes in serum electrolytes following MARS treatments. Patients in OIC group had an unfavorable outcome, with progressive deterioration of hepatic and renal function, and death within 10 days after mushroom ingestion.

Discussion

FLF resulting from different causes (viral hepatitis, paracetamol overdose, toxins from the A. phalloides) remains one of the most critical issues in the discussion of appropriate treatment options. Multiple medical complications and multi-organ failure can result from severe acute LF. These include acute renal failure (ARF) and respiratory failure, severe sepsis, disseminated intravascular coagulation, acute HE and significant hemodynamic derangements (Sherlock & Dooley, 1993; Tan, 2004). Morbidity and mortality due to mushroom poisoning are common occurrences in Eastern Europe, including Romania (Lionte et al., 2002). Mushroom poisoning also represents a problem in the United States (Donnelly & Wax, 2005). The clinical syndrome associated with A. phalloides poisoning can be characterized by four stages (Table II.5).

Table II.5. Clinical picture of Amanita Phalloides poisoning. (Sorodoc, Lionte et al., 2011)

Stages	Clinical and biological features
1. Incubation phase – 8–12 h after ingestion	Asymptomatic.
2. Gastrointestinal stage (frequently misdiagnosed as viral gastroenteritis) – 6–40 h after ingestion	Abdominal cramps; Profuse watery diarrhea; Vomiting.
3.Cytotoxic or parenchymatous stage	Jaundice, encephalopaty, oligoanuria; Liver function tests, coagulation studies, and serum creatinine rapidly become abnormal.
4. Comatose stage	Acute tubular necrosis, and subsequent renal failure, followed by respiratory failure, hemorrhage, causes death by days 4–7.

All six patients included in study had typical features of A. phalloides poisoning at the moment of hospital admission. Amatoxins represent the most important toxins that induce A. phalloides poisoning, because they interfere with DNA transcription by inhibiting RNA polymerase B. Synthesis of messenger RNA and subsequent protein synthesis is interrupted, that is why the gastrointestinal tract, the liver and the kidneys (where there are cells with high rates of protein synthesis) are particularly sensitive to injury (Faulstich, 1979). A single mushroom weighing about 50 g (which contains 5–7 mg amatoxin) can produce severe poisoning, the lethal dose of amatoxins being of approximately 0.1 mg/kg (Himmelmann et al., 2001; Vesconi et al., 1985). The patients included in the study presented typical clinical

features of A. phalloides poisoning, they consumed various amounts of mushroom meal (50 to 250 g), but dosage of alpha-amanitin was technically impossible (our laboratory could not perform this assay). We determined initial levels for PT/PTT, AST/ALT and CBC with platelets, BUN and creatinine, as well as clotting factors, particularly Factor V, because it seemed to have some prognostic significance (Christen et al., 1993). Blood glucose and ammonia levels were closely monitored. Active urinary sediment may signal the onset of acute tubular necrosis (Zawadzki et al., 1993).

Initial therapy in our patients with A. phalloides poisoning consisted of gastric lavage, intensive intravenous fluid resuscitation and multiple doses of activated charcoal with a cathartic to remove all remaining stomach contents and to draw the toxin from the entero-hepatic circulation. We performed continuous nasoduodenal (ND) aspiration with an ND tube as recommended (Scheurlen et al., 1994). A number of drugs have been trialed with varying success in A. phalloides ingestions, such as penicillin G (for its ability to displace amanitin which exists bound to plasma protein sites and promotes its excretion, for prevention of hepatic uptake of the amatoxin, and its value for inhibiting the toxin's cellular penetration), and silibinin (competes with amatoxins for transmembrane transport, and inhibits the penetration of amanitin into hepatocytes, thus having direct hepatoprotective effect). Other pharmacological agents used without proven efficacy and various degrees of success have been thioctic acid, steroids, vitamin C, N-acetylcysteine and cimetidine (O'Brien & Khuu, 1996). In our patients, we used penicillin G, silymarin, thioctic acid and N-acetylcysteine in doses recommended in literature. Vitamin K and fresh frozen plasma were given to temporarily supplement clotting factors in severe coagulopathy. Our patients had no improvement in clinical and biochemical evolution, or mortality, despite OIC.

Orthotopic LT should be considered in patients with criteria listed in Table II.6. Nevertheless, its use is limited by organ donor shortage, especially in countries like Romania where the supply of livers suitable for transplantation is limited and unpredictable.

Table II.6. King's College Hospital criteria for LT in patients with non-acetaminophen – induced FLF (adapted from Sherlock & Dooley, 1993)

All patients with:	Patients with any three of the following variables, irrespective of HE grade
Prothrombin time >100 seconds, irrespective of HE grade.	Age <10 or >40 years; Aetiology – non-A, non-B hepatitis, halothane hepatitis, severe idiosyncratic drug reactions, Amanita phalloides poisoning; Duration of jaundice before onset of encephalopathy > 7 days; Prothrombin time >50 seconds; Serum bilirubin > 300 μmol/L.

Only 10% of patients with LF are transplanted because of the limited availability of donor organs. The inability to control cerebral edema and the occurrence of multiple organ failure precludes the use of transplantation for the treatment of these patients (Stange & Mitzner, 1996). Despite the improvements achieved in the treatment of LF, the mortality rate remains unacceptably high, ranging from 40% to 80% (Rahman & Hodgson, 2001; Stockmann & Ijzermans, 2002). FLF complicated by ARF is associated with almost 100% mortality (Bernuau & Benhamou, 1991). Our patients with both LF and ARF had also 100% mortality, in the absence of MARS therapy (cases 4–6).

An integral strategy of management of these patients is to optimize patients' medical condition, either in anticipation of LT in FLF patients or of spontaneous liver recovery. OIC and the use of extracorporeal liver assist devices, which provide acute temporary liver support, remain the cornerstone of medical treatment for such patients (Tan, 2004). Stange and Mitzner developed MARS system, a blood detoxification method for protein-bound substances, as well

as water-soluble toxins, through the dialysis component (Mitzner et al., 2000; Jalan et al., 2004; Steiner & Mitzner, 2002). Substances removed by MARS include ammonia, bilirubin, free fatty acids and aromatic aminoacids (Awad et al., 2001). Improvements in the clinical parameters of cerebral function following MARS treatment may be due to the removal of mediators like ammonia and other protein-bound liver toxins (Jalan & Williams, 2001). This might explain why the third case in our study became conscious after 2 MARS sessions. Other toxins that seemed to be removed during MARS include BUN and creatinine, which is the basis of the beneficial effect of MARS in patients with concomitant acute LF and ARF (Stange & Mitzner, 1996; Kamath et al., 2001; Kreymann et al., 1999).

Patients in our MARS group had an immediate improvement in biochemical parameters: drop of ALT, bilirubin and ammonia levels, and significant improvement of PT and creatinine after MARS sessions. The OIC group failed to improve their biochemical tests.

Albumin dialysis with the MARS system has been clinically used as a liver support device in more than 3,500 patients with acute LF of various etiologies, hepato-renal syndrome, primary non-function after LT, or an acute decompensation of a chronic LF worldwide until now (Lionte et al., 2005; Stange & Mitzner, 1996; Stockmann & Ijzermans, 2002; Kapoor et al., 2000; Mitzner et al., 2001; Kellersmann et al., 2002; Sorkine et al., 2001; Voiculescu et al., 2002). With regard to LF secondary to mushroom poisoning, we found only 10 reports in PubMed, and only four of these were presentations of case series in adults.

We reported the first Romanian case series of MARS technology used in adults with A. phalloides-induced FLF. In our study, MARS sessions were well-tolerated and led to clear-cut clinical improvement in the liver, neurological and general condition in one of three patients. Patient 1 in MARS group was admitted 4 days after mushroom ingestion, developed cardiopulmonary arrest, with cardiopulmonary resuscitation before MARS could be initiated, and despite OIC and MARS sessions, the subject died. Case 2 had a delay in initiation of MARS therapy caused by technical difficulties and developed rebound in bilirubin level after MARS-1 and persistently low PT, which represented negative prognostic markers in our series, as well as in other series of patients treated with MARS (Covic et al., 2003). Case 3 was the only survivor in the MARS group, and the small quantity of mushroom meal ingested (50 g) compared with the other patients (150–200 g) could be in favor of this outcome, together with favorable evolution of all biochemical parameters, especially PT and bilirubin after MARS sessions. Our study revealed that though there were no significant statistical differences between the two groups analyzed concerning age, body mass index, approximate amount of mushroom meal ingested, time to hospital admission, vital signs at presentation, initial MELD or Glasgow coma score, or time of death after mushroom ingestion, MARS therapy alone significantly increased hospitalization time in ICU, significantly improved biochemical parameters and decreased mortality rate. Our results regarding mortality rate were higher than those reported in other series of cases, probably because of the small number of patients analyzed (three consecutive patients over 3 months), the sex of the patients, because feminine gender is a predictive factor for a fatal outcome (Escudié et al., 2007), delay in MARS initiation from mushroom ingestion (104 ± 16.09 hours) and impossibility of LT. Faybik reported six consecutive patients with A. phalloides-induced LF, with an average 76-hour delay to MARS, 16.66% mortality rate, but three patients received also LT (Faybik et al., 2003). Another study presented 10 patients analyzed over 7 years, with an average 48-hour delay to MARS, 0% mortality rate, but one patient had also LT (Kantola et al., 2009).

Early initiation of MARS in severe FLF secondary to mushroom poisoning in adults, as well as a longer duration of MARS sessions, could reduce the number of MARS sessions required, prevent irreversible liver deterioration or life-threatening complications and avoid liver transplantation (Sein Anand et al., 2007; Hydzik et al., 2005; Faybik et al., 2003; Kantola

et al., 2009). We recommend that the MARS therapy should be used in the treatment of A. phalloides-induced FLF as part of a randomized controlled trial for MARS evaluation in mushroom-induced LF.

Conclusions

MARS is a safe, homeostatic tool and highly effective depurative therapy in adults with A. phalloides-induced LF. Survival is predicted by the initial impact of MARS therapy, amount of mushroom meal ingested and time to MARS initiation. Rebound in bilirubin level after MARS and persistently low PT represent negative prognostic markers in A. phalloides-induced FLF. MARS in association with OIC decreases mortality rates, but does not guarantee survival and recovery in all cases.

II.3. The role of neutralizing therapies in organophosphate poisoning.

This direction of research is reflected in the following published articles:

1. Petriș OR, Gazzi E, Șorodoc L, Bologa C, Șorodoc V, **Lionte C**. Assessing the capacity of various substances to act as neutralizing treatment in organophosphoric acute intoxications. *Rev Chim (Bucharest),* 2015; 66(2): 230-232. **(IF 0.956)**

Background

Controversial data persist in the literature regarding activated charcoal capacity to bind organophosphates (Lheureux & Askenasi, 1992). Some accept its use as a potent therapy but other researchers have failed in proving any binding capacity that it might exert regarding organophosphates. Due to its large utilization in Poisons Centers for binding other kind of toxics, its availability and routine in administration, lack of known related adverse reactions, ease of administration using an already placed tube at gastric level (necessary for the performance of the gastric lavage) its use is largely encountered in medical practice (Van Hoving et al., 2011).

Over time, many substances have been proposed as neutralizers: sodium bicarbonate, alginate etc. stressing that a major chapter from the management of organophosphates poisoning – neutralization – is still incompletely exploited through the existent substances (Tuncok et al., 1995). Neutralization represents an important goal in toxicology, the reduction of poison exposure being crucial in any management plan of any intoxication (Coruzzi, 2010). Situations of poison that remain in an active form in the body make its absorption to persist and the therapeutic maneuvers to fail.

Aim of the study

Due to the fact that, in our study, we intend to analyze the capacity of certain substances to bind organophosphates and not, at this stage, the way in which this binding occurs, we will refer to this effect with the general term of neutralization although we are aware of the preexisting concepts of *neutralization* – chemical interaction that led to poison inactivation and *decorporation* – physical and chemical interaction with the toxic leading to his elimination (An et al., 2017).

Materials and methods

The substances believed to possess neutralizing capacities were included in the study after revising specialized literature (Eddleston et al., 2008), consultative brainstorming discussions with specialists from the "Petru Poni" Institute of Macromolecular Chemistry of

Iasi, Department of Chemistry from the "Al. I. Cuza" University of Iasi, Institute of Public Health of Iasi and from the Department of Pharmacology and Toxicology of the "Grigore T. Popa" University of Medicine and Pharmacy Iasi. Restricted by the availability of the selected substances, a list of them was conceived. The substances were afterwards grouped based on their water solubility. For those insoluble in water an in vitro experiment was designed in order to assess their capacity of binding organophosphates.

Materials

1. Trichlorfon – produced by SC Chimcomplex SA Borzesti, 90% purity, wettable powder war used (dose: 200 mg/kg body weight).
2. Hydrophobic substances to act as neutralizers in acute organophosphate intoxication:
   - Dextran – as microparticle – polysaccharide with a branched structure suitable for absorption processes.
   - Medicinal charcoal – largely used until few years ago, because of its similar name with the activated charcoal and the low availability of the last one.
   - Activated charcoal – largely accepted for neutralization of poisons, has no proof of associated benefits for organophosphates intoxication.
   - Eucarbon® – a type of vegetal charcoal that is considered to be superior to medicinal charcoal in its medical indications (constipation etc.).
   - Lysozyme - lysozyme fixed on an organic support.
   - Activated fluorisil – also a mineral compound, similar to charcoal (requiring also activation), used in gas chromatographic methodology of organophosphate isolation (organophosphates being retained by fluorisil). In case of positive results, it could be incorporated in the filters used in gas masks or in other devices supposed to work in dry conditions).
   - Beta-cyclodextrin – natural polymers with binding capabilities with molecular conformations that mimic the aspect of a bucket in which various components can be included.
   - N vinyl polybenzimidazole – benzimidazole having studies indicating organophosphate binding capabilities but also carcinogenic effects. Integration in a non-resorbable polymer could constitute a solution for human usage (Gungordu et al., 2013; Craciun et al., 2013).
   - Plasma–dextran – in order to use the existent useful compound from plasma (hydrolases, serum cholinesterase, proteins etc.) capable to neutralize organophosphates, plasma was bound on micro particles of dextran. The resulted complex was thought to resist digestion inside digestive tract without secondary absorption of the released toxic.
   - Others: silica gel – a siliceous derivate; celite (alumina) – aluminum trioxide; aluminum monoxide; Sephadex G – a dextran with high level of reticulation; C18 – siliceous powder used in gas chromatography as absorbent material that captures organophosphate at filter cartridge level.

Experimental part

0.5 g of each analyzed substance was individually placed in a tube of 30 mL volume with glass stopper in which the level of 10 mL was previously marked. In each tube, by pipetting, distilled water was added until the level of 10 mL was achieved. By doing so, each tube contained a volume of 10 mL total in which 0.5 g of substance was mixed with water. Fourteen test tubes resulted and were numbered according to the number of the studied neutralizer contained within.

In the morning of the experiment the total necessary quantity of Trichlorfon was weighted at the analytical balance for a 0.2 g per sample. 0.2 g multiplied with 15 (14 substances plus one control) gave the final quantity of 3.3 grams commercial Trichlorfon.

Trichlorfon 90% ---> 90 g pure Trichlorfon…….100 g commercial Trichlorfon

0.2 g……..x

x =100/90x0.2 =0.22; 0.22 x 15 = 3.3g commercial Trichlorfon.

For Trichlorfon the solution was used in a total volume of 10 mL per each sample leading to a total volume of 10 x 15 samples = 150 mL final volume. 3.3 g commercial Trichlorfon were weighed and placed in a 150 mL flask fitted with a glass stopper and a small volume of distilled water was added. By shaking the flask which was fitted with the glass stopper, at room temperature, the Trichlorfon powder was completely dissolved. After that the flask was filled with distilled water until the sign, to a final volume of 150 mL.

By pipetting, 10 mL of this solution were transferred in each 14 of the previously prepared tube. The remaining 10 mL were placed in a new tube to which 10 mL of distilled water was added to form the control, which was numbered 15. All the 15 tubes were kept in the same conditions of temperature and humidity as the rest of the samples: 4 h in a thermostatically controlled water bath at 37°C and shaken by placing the pan on a shaking plate system. The resulted suspensions were after that filtered using a glass funnel with a valve, inside of which a filter paper was placed. The valve was necessary to recover the liquid resulted after filtration in the same glass tube in which the suspension was prepared. In order to recuperate all the Trichlorfon that was not retained by the analyzed neutralizer, the filter paper was washed after that with a supplementary volume of distilled water, collected also in the correspondent glass tube, until a total final volume of 20 mL per tube. By doing so, at the end, we have obtained a 20 mL volume of solution in all the 15 tubes (14 samples and one control) and we have avoided situations in which the final concentration of Trichlorfon to be even higher than the control. This situation could appear if the analyzed substance binds only water, thus increasing the concentration of Trichlorfon. Gas chromatography (Wollersen & Musshoff, 2007) was used to assess the content of Trichlorfon in the analyzed solutions.

Results and discussions

The gas chromatography method that we used involves an error interval until 10 % so those differences were not taken into account at the final analysis. A clear effect of binding with Trichlorfon was proven only for activated charcoal, medicinal charcoal, and C18 (Figure II.10, Table II.7).

Activated charcoal was proven to bind Trichlorfon but in a low efficiency manner. 1 gram of activated charcoal appears to bind only 0.065 g of Trichlorfon (Table II.7).

For only 5 g of Trichlorfon the necessary quantity of activated charcoal already equals the routinely used 1 g per kg body weight in a poisoned patient of 75 kg. The necessary quantity is almost diminished to half if medicinal charcoal is used. This appears to be a more available, and the least expensive solution for this type of intoxications.

The most powerful binding effect was retrieved for C18, only 22.5 g of this substance being necessary to completely bind 5 g of Trichlorfon. In this respect until the dose of 1g/kg body weight, a good interval for therapeutic efficiency is obtained.

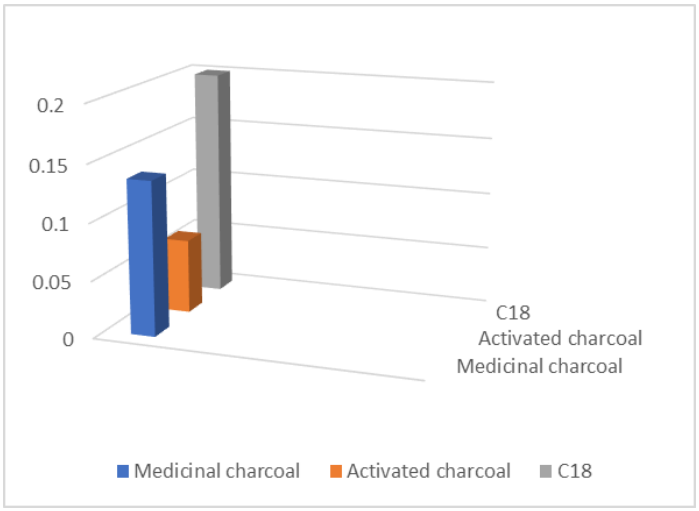


Figure II.10. Binding capacity for Trichlorfon of the substances with a neutralizing effect.

Table II.7. Binding capacity for Trichlorfon, of the substances included in the study.

Studied substance			Etalon of Triclorfon		Binding capacity	
Name:	utilised quantity (grams)	GC signal amplitude (mm)	utilised quantity (grams)	GC signal amplitude (mm)	degree (%) of GC signal reduction	quantity of Triclorfon neutralised by 1 gram of substance (grams)
1. Plasma + dextran	0.5	121	0.2	122	100-99.2=0.8	-
2. Dextran	0.5	121	0.2	122	100-99.2=0.8	-
3. Activated charcoal	0.5	102	0.2	122	100-83,6=16.3	0.065
4. Medicinal charcoal	0.5	118	0.2	178	100-66.3=33.7	0.135
5. Eucarbon	0.5	117	0.2	122	100-95.9=4.1	-
6. Fluorisil	0.5	168	0.2	178	100-94.4=5.6	-
7. Nvinilpoli-benzimidazol	0.5	119	0.2	122	100-97.6=2.4	-
8. Lysozyme	0.5	122	0.2	122	100-100=0	-
9. βciclodextrine	0.5	121	0.2	122	100-99.2=0.8	-
10. Silicagel	0.5	168	0.2	178	100-94.4=5.6	-
11. Celite	0.5	168	0.2	178	100-94.4=5.6	-
12. Aluminium oxide	0.5	168	0.2	178	100-94.4=5.6	-
13. Sephadex G	0.5	174	0.2	178	100-97.8=2.2	-
14. C18	0.5	26	0.2	52	100-50=50	0.2

Conclusions

Many of the analyzed substances (dextran, Eucarbon®, Lysozyme, activated fluorisil, beta- cyclodextrin, N vinyl polybenzimidazole, plasma-dextran, silica gel, Celite, aluminum monoxide, Sephadex G) were proved to have no binding effect to Trichlorfon. The maximum efficiency was obtained for C18, a siliceous powder used in gas chromatography as absorbent material to capture organophosphate at filter cartridge level, which binds 0.2 g of Trichlorfon per each gram of C18. For the activated charcoal, a binding capability was observed, but reduced and its use in medical practice, based on its availability and lack of side effects, could be substituted by the administration of medicinal charcoal, in the acute intoxication with organophosphate substances. Further studies are necessary to detect a better neutralizing agent in organophosphate acute poisoning by ingestion.

III. DIAGNOSIS AND THERAPUUTIC CHALLENGES IN MEDICAL EMERGENCIES AS A CONSEQUENCE OF DRUG OVERDOSE OR POISONING

III.1. The effects of exposure to drugs in therapeutical dose and/or overdose

The term overdose implies intentional exposure to a drug or toxin, such as suicide attempt or illicit drug abuse. The term poisoning implies a clinical symptomatology, and also an unintentional exposure to the toxin (Shannon, 2007). Poisoning is a quantitative concept. Any pharmaceutical or non-pharmaceutical substance at some specific dose and time is harmless, while the same substance at other doses and time is toxic. While dose is the primary determinant of toxicity, effects of non-pharmaceutical agents on the body are also dependent on the length of time in which such substances are present. An internist working in an emergency hospital is involved in the diagnosis and management of such patients, along with specialists in Emergency Medicine and Intensive Care, because such patients, after initial evaluation in the Emergency Department (ED), are admitted either in ICU, or in an internal medicine ward.

Acute poisonings represent an important cause of mortality and a challenge to the ED in many countries. The majority of cases presented to the ED are self-poisonings, and the substances which have been causing severe outcomes for the past decade are antidepressants, stimulants and street drugs, antihistamines, and anticonvulsants (Gummin et al., 2019). Nevertheless, acute toxicities after pesticide exposure globally account for the overwhelming majority of poisoning deaths (Senarathna et al., 2012). Up to 40% of the patients visiting the ED with an intoxication are admitted to the hospital, and an average of 1.5–3.7% poisoned patients need intensive care unit (ICU) admission (Brandenburg et al., 2017). In our area, epidemiological data suggested that 97.27% are acute drug poisonings in suicide attempts, using mainly combinations of drugs (32.92%), with a mortality rate of 0.3% (Sorodoc et al., 2011).

Recognition of poisoning and drug overdose requires a high index of suspicion and a careful clinical evaluation. Even though they may not appear to be acutely ill, all poisoned patients should be treated as if they have a potentially life-threatening intoxication. Along with conventional laboratory tests, qualitative and quantitative toxicological tests might identify the offending substance, but they do not contribute to the management of the poisoned patient. The general approach in the case of a poisoned patient uses both routine laboratory tests and, in some circumstances, specific biomarkers developed for cardiac emergencies (troponins, cardiac enzymes, and natriuretic peptides). However, all poisoned patients should be treated as if they have a critical condition, with many steps to be performed simultaneously (e.g., airway management, antidote such as naloxone and dextrose administration, and decontamination measures) during initial evaluation (Olson, 2004).

Rhabdomyolysis is a syndrome that is characterized by necrosis of the skeletal muscle tissue and consequent release of cellular byproducts into the blood. From all the released components, the most dangerous is myoglobin, which can cause acute renal failure via its direct toxicity to the renal tubules. Rhabdomyolysis can be a consequence of various causes, which include genetic and metabolic myopathies, trauma, infections, electrical injuries, hyperthermia, autoimmune disorders, and adverse drug interactions (Allison & Beosole, 2003).

The diagnosis and management of patients with an abnormal ECG encountered in a specific toxicity can challenge experienced physicians. One must have serious knowledge of basic cardiac physiology in order to understand the ECG changes associated with various drugs and toxins (Lionte et al., 2012). Myocardial injury frequently occurs after exposure to pharmaceutical agents with a recognized cardiotoxicity, toxic gases, pesticides, drugs of abuse, or vegetal toxins, and it was proved to be a predictor of mortality (Hassanian-Moghaddam et

al., 2014). When occurring in acute poisonings, cardiovascular complications, especially dysrhythmias, lead to poor outcomes, even death (Hoffman et al., 2007).

The syncope is a situation commonly encountered in medical practice, it leads to disabilities, it may be associated with sudden cardiac death (SCD) risk, and its causes are difficult to identify. Toxic-induced syncope (TIS) is a topic rarely reviewed in literature, only isolated cases being reported (Yilmaz et al., 2006; Onvlee-Dekker et al., 2007; Guha et al., 1999), that is why we attempt to cover all practical issues regarding this condition.

Metabolic consequences of drug overdose and toxin exposure might complicate the evolution and prolong hospitalization. Hyper- and hypoglycemia are common problems in hospitalized patients with or without a history of diabetes mellitus (DM). Hyperglycemia might exert an even more deleterious effect on those patients without DM than among patients with DM during acute illness (Zaccardi et al., 2018**;** Krinsley et al., 2009). The cause of drug-induced pancreatitis (DIP) involved at least 40 of the top 200 most prescribed medications (Kaurich, 2008). DIP is considered to be rare (2%), and to make the diagnosis, other possible causative factors must be ruled out (Mallick, 2004).

Food poisoning was another area of my research. Scombroid poisoning is a clinical syndrome resulting from food consumption, especially Scombroidea fish (e.g. tuna, mackerel, albacore, bonito) or nonscombroid fish (mahi-mahi, amberjack) and cheeses that contain unusually high levels of histamine (Borade et al, 2007). Although outbreaks of scombroid fish poisoning are frequently reported in Japan, Canada, United States, and other countries with a high dietary intake of fish (Kow-Tong et al., 1987), few cases are reported in Europe (Ascione et al., 1997). We described for the first time a series of such cases in Romania. More than 90% of all fatal cases of mushroom poisoning are secondary to A. phalloides (Donnelly & Wax, 2005). Its rapid evolution towards fulminant liver failure (FLF) makes poisoning with A. phalloides a medical emergency. The development of acute tubular necrosis, and subsequent renal failure worsening liver failure (LF), and rising ammonia levels cuase hepato-renal syndrome, hepatic coma and convulsions, followed by respiratory failure, hemorrhage, and death from 6 to 16 days after the onset. Despite significant advances in intensive care management of A. phalloides-induced FLF, patients with this condition still have a high mortality rate in the absence of orthotopic liver transplantation (Lionte et al., 2002).

There are many differences with respect to the pattern and cause of acute poisoning between geographical regions, even within the same country, and there is a constant need for new information in this field in order to develop educational and prevention programs (Islambulchilar et al., 2009). The number of deaths from accidental poisoning in enlarged European Union (EU 25) was 10,194 in 2005, which represents 4.4% of deaths due to external causes. Age-standardized death rate (SDR) for accidental poisoning was 2.1 for 100,000 inhabitants in 2005, among the 25 countries of the EU (Belanger et al., 2008).

Few epidemiological studies concerning acute poisoning exist in Romania, and they are exploring mainly pediatric poisoning (Nistor et al., 2018). Identifying the epidemiological and evolutionary aspects of acute intoxications must be a major objective for the health system, given that this pathology can be at least partially avoided and its incidence and severity may be reduced using appropriate measures. First studies on the epidemiology of acute drug and organophosphate poisoning in adults in this region has been published in an international medical journal only after the research conducted by our team.

Our research provided significant information concerning the pattern of acute poisonings in North-Eastern Romania. These data underline that, in order to provide a proper management of drug poisonings, a Regional Poison Information Center is absolutely necessary.

III.1.1. Drug-induced rhabdomyolysis

This direction of research is reflected in the following published articles:

1. Petrov, M; Yatsynovich, Y; **Lionte, C.** An unusual cause of rhabdomyolysis in emergency setting: challenges of diagnosis. *Am J Emerg Med* 2015; 33(1): 123.e1–123.e3. doi:10.1016/j.ajem.2014.05.041 (**FI 1.504**)
2. **Lionte C**, Sorodoc L, Petriș O, Sorodoc V, Bologa C, Anton G. Non-traumatic rhabdomyolysis in medical practice. *Rev Med Chir Soc Med Nat Iasi*. 2009;113(4):1025-33. (ISSN: 0048-7848) **PMID: 20191869**

Introduction

Rhabdomyolysis is a syndrome that is characterized by necrosis of the skeletal muscle tissue and consequent release of cellular byproducts into the blood. From all the released components, the most dangerous is myoglobin, which can cause acute renal failure via its direct toxicity to the renal tubules (Warren et al., 2002). Rhabdomyolysis can be a consequence of various causes, which include genetic and metabolic myopathies, trauma, infections, electrical injuries, hyperthermia, autoimmune disorders, and adverse drug interactions (Allison & Beosole, 2003; Lionte et al., 2009). Rhabdomyolysis ranges from an asymptomatic illness with elevation in the creatine kinase level to a life-threatening condition associated with extreme elevations in creatine kinase, electrolyte imbalances, acute renal failure and disseminated intravascular coagulation – DIC (Zager, 1996). The most common causes of rhabdomyolysis in general practice are represented by muscular trauma, muscle enzyme deficiencies, electrolyte abnormalities, infections, drugs, toxins and some endocrinopathies. Frequently encountered clinical manifestations are weakness, myalgia and tea-colored urine, and the most sensitive laboratory finding of muscle injury is an elevated plasma creatine kinase level (Sauret et al., 2002). The management of patients with rhabdomyolysis includes early vigorous hydration, together with urine alkalinization, mannitol, hemodialysis (Huerta-Alardin, 2005).

Aim of the study

The aim of this study is to determine frequency and causes of rhabdomyolysis in internal medicine practice, as well as diagnostic and therapeutic challenges, based on a retrospective study on patients admitted to a medical clinic of a university emergency hospital as well as significant clinical cases.

Materials and methods

A retrospective study on patients admitted in an Internal Medicine Department of an Emergency Hospital over 24 months was conducted, including 4,027 patients admitted for medical emergencies. The evaluation included complete clinical examination with focus on signs and symptoms suggestive for a rhabdomyolysis, such as myalgia, muscle weakness, edema of the muscles (even in the absence of skin color changes), oligo-anuria, and/or tea-colored urine, fever > 38ºC, and prolonged coma. Upon admission, patients took blood tests in order to determine the following tests: creatin kinase (CK), glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), lactate dehydrogenase (LDH), blood ureea nitrogen (BUN), creatinine, uric acid, electrolytes, alkali reserve. Patients with a diagnostic of myocardial infarction, recent surgery, polytrauma, chronic renal failure were excluded from the study. Patients with a CK level > 5 times the upper reference limit (URL), which defines rhabdomyolysis, were monitored with regard to daily urinary output, evolution of CK levels and occurrence of complications: electrolyte disturbances (hipocalcemia, hyperkalemia),

hepatic cytolysis, cardiac arrhythmias, acute kidney failure, DIC. We also reported the second case in literature of a trimethoprim-sulfamethoxazole (TMP-SMX)–induced rhabdomyolysis in an immunocompetent patient, possibly aggravated by a drug interaction with nonsteroidal anti-inflammatory drugs (NSAIDs). Data are expressed as percentage (%) and mean ± standard deviation (SD).

Results

From the 4,027 patients admitted in the Internal Medicine Department in a 24-month timeframe, 72 presented with an altered level of conscience (1.78%), and 16 patients presented signs of rhabdomyolysis (nine women and seven men), and were included in the analysis. The prevalence of patients with laboratory criteria of rhabdomyolysis was 0.39 % in the population admitted in the Internal Medicine Department during the study. The age of the included patients was 44.43±17.02 years. The causes of rhabdomyolysis are presented in Figure III.1 and associated comorbidities in Figure III.2.

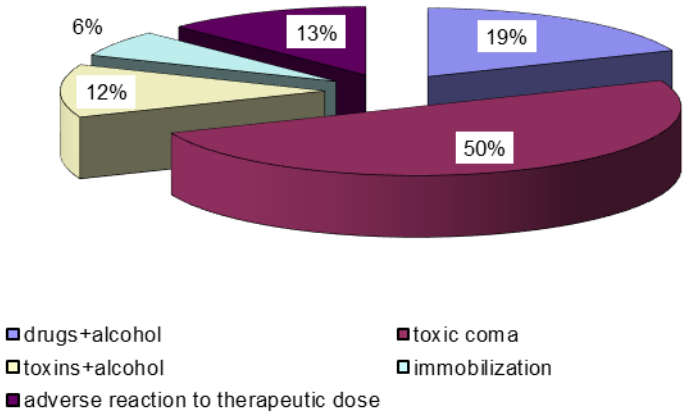


Figure III.1. The main causes of nontraumatic rhabdomyolysis.

81.25% patients had a diagnosis of acute poisoning, four of them had acute mixed intoxications. The drugs involved were barbiturates, benzodiazepines, neuroleptics, antiepileptic drugs, phenotiazines, antipsychotic drugs, opiates, statins and NSAID's, while toxins involved were represented by ethanol, organophosphates, raticides and organic solvents (chloroform, acetone). One patient was admitted for a minor stroke and had rhabdomyolysis as a result of mixed causes, such as chronic drug intake and prolonged immobilization. Another case presented with rhabdomyolysis after atorvastatin 10 mg/day prescribed for hyperlipoproteinemia, and one patient developed rhabdomyolysis after strenuous physical activity and self-medication with NSAID's (meloxicam, ketorolac, ibuprofen). Among patients admitted with an altered mental status, 16.7% patients had rhabdomyolysis. Mortality rate was 12.5%. General signs (fever, dehydration, hypotension) and urinary signs (dark urine, anuria) were present in 68.75% patients. Specific muscle signs for rhabdomyolysis were reported in 50% cases, and consisted of myalgias, muscle rigidity, weakness, cramps (Table III.1). CK peaked from the first day of admission in all patients, the maximal values were 23,988 ± 32,765.91 U/L. Uric acid was increased in 50% patients (7.63 ± 0.38 mg/dL). Electrolyte disturbances recorded were hyperkalemia (43.75%), mild hyponatremia (31.25%) and hypocalcemia (25%). 37.5% patients developed acute kidney injury and two patients had an unfavorable outcome, with multiple complications and death. Metabolic acidosis was recorded in 10 cases (62.5%). Liver complications were recorded in 4 patients, and DIC was present in only one deceased patient.

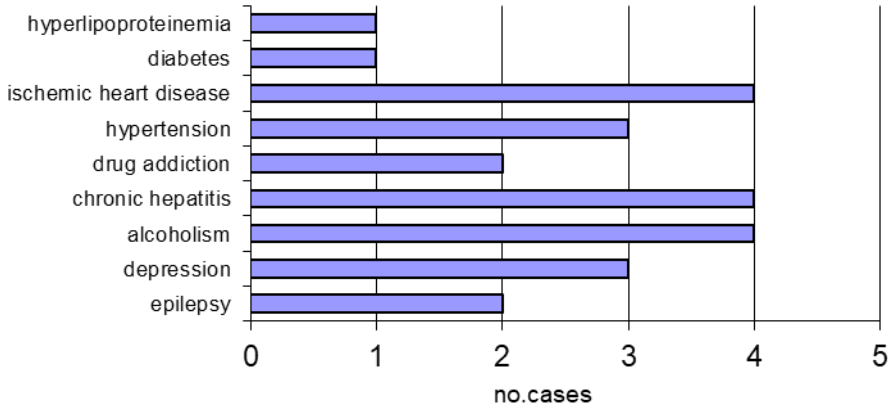


Figure III.2. Associated comorbidities in patients with nontraumatic rhabdomyolysis.

Table III.1. Clinical picture and laboratory data in patients analyzed.

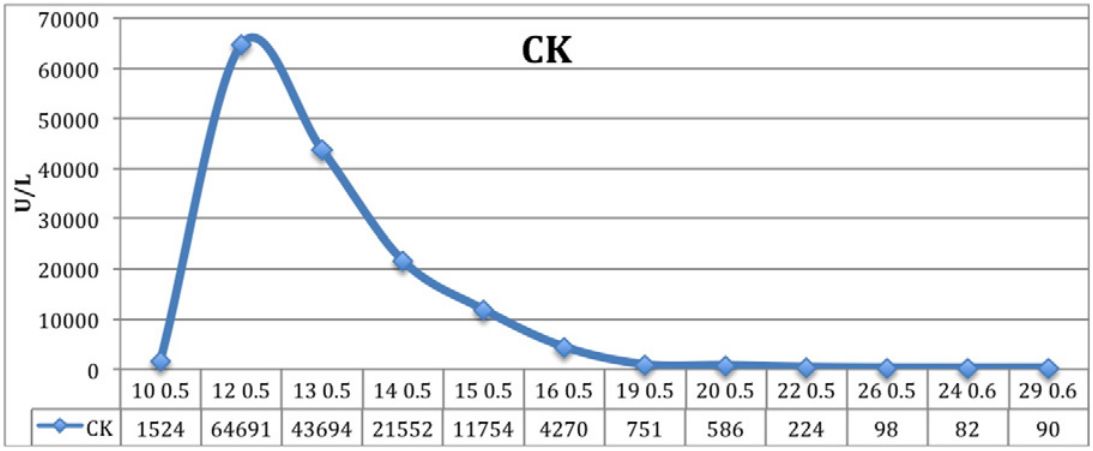
Case no.	GCS score	Muscle signs/symptoms	Urinary signs	CK** (NV: 30-150 U/L)	Creatinine** (NV: 0.6-1.3 mg/dl)
1	12 (o)	-	-	1814±948.93	1±0.28
2	5 (c)	#	*	9201.5±10184.45	1.45±0.91
3	6 (c)	-	*	4816.5±5503.41	1.05±0.21
4	6 (c)	#	*	8312.5±10287.69	2.3±2.40
5	4 (c)	#	*, &	6819±8564.47	2.15±2.19
6	11 (s)	-	-	1580.5±1099.55	1.1±0.14
7	11 (s)	-	*	9726±12511.54	1.9±0.56
8	5 (c)	#	*	12667.5±14272.95	1.3±0.70
9	4 (c)	#	-	27839±12067.48	1.4±0.56
10	6 (c)	-	*, &	23988±32765.91	2.4±1.83
11	13	-	-	1766.5±448.79	0.85±0.21
12	13	-	-	1053.25±532.34	1.2±0.17
13	4(c)	#	*	4986.2±3055.65	0.8±0.14
14	11 (s)	-	*	1089±567.85	1±0.1
15	15	#	*	2571.33±2566.21	0.7±0.1
16	15	#	*	16560.66±23048.72	0.86±0.26

(o) – obtundation; (c) – coma; (s) – stupor; *, dark urine; &, anuria; #, myalgia, rigidity, weakness, cramps; **, mean±SD

Other recorded complications were: arrhythmias (paroxysmal atrial fibrillation, premature ventricular beats) – 2 cases, bronchopneumonia/pneumonia – 3 cases, and paresis nerve sciatic right external popliteus – one case. Four patients had a simple evolution, without complications. Mean hospitalization length was 9.4 ± 5.45 days, and deaths were recorded after three and respectively four days after admission.

The significant case reported was of a 64-year-old man, 45-pack/year smoker, with no significant family history and a past medical history of urethral polyps, who was admitted to the hospital due to a worsening bilateral lower extremity pain, severely disturbed walking, and tea-colored urine. Patient stated that, 2 days earlier, he sought medical attention in the emergency department (ED) for the same pain and darkening of urine that have become more prominent over the past 7 days. Further from his history, we learned that he self-medicated with Biseptol® (TMP-SMX 40/800 mg) 3 tablets per day for 2 weeks due to a "self-diagnosed" urinary tract infection (UTI). He explained that he previously had an UTI, and a physician prescribed him a TMP-SMX treatment, which cured the infection. When he experienced the same symptoms, he obtained TMP-SMX and self-medicated for a period of 2 weeks with a

dosage as stated above. During therapy, he began to experience lower extremity pain. Pain was gradual and increasing in intensity, for which he sought medical attention in an ED. The analyses showed an aspartate aminotransferase 66 U/L, creatinine kinase–MB 69 U/L, and an increased creatinine kinase (CK) level of 1524 U/L (reference range, 30-170 U/L). He was referred to a neurologist, who suspected polymyositis and scheduled an appointment for further investigations in 2 days. During this time, the pain became more intense, and he decided to take some painkiller medication, which included ibuprofen 200 mg per day, celecoxib 200 mg per day, piroxicam 20 mg per day, Algocalmin® (sodium metamizole 500 mg) 2 pills per day, and Antinevralgic® (acetyl salycilic acid 250 mg + phenacetine 150 mg + caffeine 50 mg) 2 pills per day. He also consulted a rheumatology specialist, who prescribed him parenteral NSAIDs as follows: ketolorac 30 mg/mL, 2 vials per day, and meloxicam 15 mg, 2 vials per day. Despite this treatment, the pain persisted and has become so severe that, upon seeking again medical attention, he could barely walk, having intense pain in the lumbar region and in the legs, dark urine, and oliguria. On admission, the patient was fully alert and oriented. On physical examination, his temperature was 37°C; blood pressure, 130/70 mm Hg; pulse, 90 beats per minute; and respiratory rate, 17 breaths per minute. Lower limbs showed signs of swelling and edema. The muscles of the lower back, glutes, thighs, and calves were tender to palpation bilaterally. Examination of head, eyes, ears, nose, and throat was unremarkable. The neck was supple and nontender to palpation. Patient denied any associated headache, neck rigidity, and upper extremity weakness or pain. Cardiovascular examination showed a normal S1 and S2. Lungs were clear to auscultation. No hepatomegaly or splenomegaly was identified. The initial laboratory analyses showed a CK of 64691 U/L (Figure III.3), CK-MB 600U/L, elevated transaminases, lactate dehydrogenase, mild acidosis, hyponatremia, hypocalcemia, hyperuricemia, and normal blood urea nitrogen and creatinine levels.



	10 0.5	12 0.5	13 0.5	14 0.5	15 0.5	16 0.5	19 0.5	20 0.5	22 0.5	26 0.5	24 0.6	29 0.6
CK	1524	64691	43694	21552	11754	4270	751	586	224	98	82	90

Figure III.3. Creatinine kinase levels from the time of admission until hospital day 16

Urinalysis showed presence of myoglobin. Electrocardiogram (ECG) was normal. Anti-Jo antibody and antinuclear antibodies were negative; thyroid function tests were all within normal limits. Skeletal muscle ultrasonography showed an important bilateral edema of subcutaneous tissue with a fluid collection of 17 mm in the thighs and 11 mm in the legs. Muscular fibers showed normal structure. Muscle biopsy revealed muscle fibers without striations and a loss of homogeneity. Some areas showed presence of erythrocytes, without any other inflammatory cell infiltrates. Other tests performed excluded all possible causes of nontraumatic rhabdomyolysis or myopathies, and we concluded the diagnosis of drug-induced rhabdomyolysis. Trimethoprim-sulfamethoxazole and NSAIDs were discontinued on admission, and the patient was started on aggressive hydration with glucose 5% and 10%,

saline solution 9%, mannitol, and furosemide, together with measures to correct electrolyte and acid-base disturbances. By hospital day 16, CK decreased within normal limits, patient's status markedly improved, and he no longer reported any myalgias. At discharge, a neurologic assessment showed no motor deficits and symmetrical +2 deep tendon reflexes without any superficial sensitivity modifications. Ultrasound showed persistence of a minor bilateral posterior thigh and leg subcutaneous edema.

Discussion

The incidence of rhabdomyolysis in medical practice is increasing, because the prevalence of main causes is increasing (especially acute drug overdoses and alcoholism). Diagnosis methods are improving, since now the CK level is routinely checked in the Emergency Department (ED). In the United States, the major causes of rhabdomyolysis in an urban population addressed to ED were cocaine, exertion, immobilization. Rhabdomyolysis is frequently diagnosed in patients with acute poisoning, subjected to prolonged muscle compression, in elderly patients after falls or strokes, or in patients with seizures of different causes (Gabow et al., 1982). Alcohol intake is a common cause of rhabdomyolysis (Vanholder et al., 2000; Grossman et al., 1974). In many situations of alcohol-induced non-traumatic rhabdomyolysis, patients had a history of acute ethanol poisoning, or ethanol-induced coma with immobilization (Bessa, 1995). These patients are usually diagnosed and treated in ED, as a cause of rapid onset of muscle pain and deceased urinary output (Hewitt & Winter, 1995; Sofat et al, 1999). Rarely described in literature, nontraumatic rhabdomyolysis associated with chronic alcoholism is underdiagnosed because of the insidious onset, paucity of symptoms, the absence of coma, seizures or prolonged immobilization in patients' history, also the absence of severe myalgias in clinical picture (Muthukumar et al., 1999; Qiu et al., 2004).

Our study revealed a high prevalence of acute poisoning (81.25%) and alcohol intake (31.25%) in the etiology of nontraumatic rhabdomyolysis diagnosed in patients admitted in an Internal Medicine Department, as opposed with other causes (prolonged immobilization, side effects of drugs, etc.).

In rhabdomyolysis, the release of necrotic striate muscle components (myoglobin, CK, LDH, urates, purines, K^+ and $PO4^-$) induces the alteration of plasma concentration of some inorganic and organic compounds, leading to toxic, sometimes life-threatening complications (Lopez et al., 1995). On the other side, the loss of integrity of sarcolemma will determine the passage of the water, Na^+ and Ca^{++} from the extracellular fluid to cytosol. The accumulation of large quantities of fluids in affected limbs (up to 10-14 liters) leads to shock, hypernatremia and renal failure. The hypoxic muscles release lactic acid into circulation, and its clearance is affected if the patient is hypovolemic (Gabow, 1982). Acidosis will impair a number of metabolic pathways and will aggravate hyperkalemia. In the early phase of rhabdomyolysis, calcium accumulates in the muscles, sometimes producing massive calcification of the necrotic muscles or heterotopic ossification (Zager, 1989; Holt & Moore, 2000). Both hyperkalemia and severe hypocalcemia can explain the arrythmias, muscle cramps, or seizures, which lead to a more severe muscle damage. Low urinary pH and tubular acidosis favor myoglobin precipitation into renal tubules, as well as uric acid (resulted after hepatic metabolization of nucleosides released by disintegrated myocytes) precipitation (Vanholder et al., 2000).

In acute renal failure, mechanisms explaining the occurrence of rhabdomyolysis are: renal vasoconstriction, intratubular cast formation, direct cytotoxicity of hemeproteins which is exacerbated in conditions of hypovolemia and aciduria (Sauret et al., 2002). Filtrated myoglobin precipitates into renal tubules, then is degraded with heme formation, which initiates lipid peroxidation and renal injury, and iron liberation, which catalyzes the production

of free radicals of oxygen and aggravates the ischemic lesions (Zager, 1996; Huerta-Alardin et al., 2005).

Drug-induced rhabdomyolysis is a relatively common and a well-known side effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors when used in conjunction with fibrates (Schreiber & Anderson, 2006) or even clarithromycin (Wagner et al., 2009). However, such condition is a rare complication of TMP-SMX therapy, with only a few cases having been documented. Those predisposed to develop rhabdomyolysis are immunocompromised patients. Recently, a first case has been documented in a non-immunocompromised patient (Ainapurapu et al., 2013). Our patient was immunocompetent, and he had previously been successfully treated with a standard TMP-SMX dosage and reported no symptoms. However, during the second episode of his UTI, for which he self-medicated with TMP-SMX, he began to experience muscle pain. The patient initially took NSAIDs for the pain produced most likely by the early rhabdomyolysis, and such decision further worsened his condition. His first visit to ED showed CK of 1524 U/L, and 2 days after addition of NSAIDs therapy, CK was 64,691 U/L (Figure III.3). Trimethoprim-sulfamethoxazole is a hepatic CYP2C9 inhibitor (Ho & Juurlink, 2011). Therefore, drugs that are CYP2C9-dependent increase in concentrations when administered with it. Such drugs include amitriptyline, celecoxib, diclofenac, fluoxetine, fluvastatin, glipizide, glyburide, irbesartan, ibuprofen, losartan, naproxen, phenytoin, tamoxifen, tolbutamide, torsemide, and warfarin (Schreiber & Anderson, 2006; Ho & Juurlink, 2011). Based on those findings, we hypothesize that this adverse reaction might have been produced by the drug-drug interaction with NSAIDs specifically at the levels of CYT2C8 and CYT2C9. However, further studies on this particular subject are needed.

The diagnosis of rhabdomyolysis is suggested by the triad: granulose pigmented casts in the urine, tea-colored urine, and marked increased CK. The clinical picture includes local signs and symptoms (pain, tenderness, distension, weakness, muscle contractions and ecchymoses) and systemic signs and symptoms such as tea-colored urine, fever, indisposition, nausea and vomiting, tachycardia, confusion, agitation, delirium and anuria (Poels & Gabreels, 1995). The muscle groups more often affected are calf muscles (deep venous thrombosis should be excluded) and lumbar region muscles (differential diagnosis with renal colic). The classical clinical picture is encountered in less than 10% patients. Thoracic muscles involvement leads to confusion with angina pectoris (Hoogwerf et al., 1979). More than 50% cases might not present with muscular signs or symptoms at all (Gabow et al., 1982).

In our study, 50% of patients presented muscle signs and 61.75% had also urinary signs suggestive for rhabdomyolysis. Systemic symptoms and signs were missing in 30% of patients, and 10% had only paraclinical criteria of rhabdomyolysis present, in the suggestive etiology context, but without clinical manifestations. Although clinical presentation and anamnesis might be conclusive, the positive diagnosis is made after laboratory evaluation of muscle enzymes. Myoglobin is the first which increases, disappears quickly (1-6 hours), and visible myoglobinuria (heme-positive urine without hematuria) appears when more than 100 grams of muscle is destroyed. CK has a 100% sensibility for the diagnosis. Values >1,000 U/L, with predominance of MM fraction, in the absence of the myocardial or cerebral infarction signifies an important muscle destruction. The maximal value is reached within 24-48 hours, and persistence or further increase in CK confirms continued damage, possible acute kidney injury (AKI). CK level is not predictive for AKI, although values of CK > 16,000 suggests a high risk for AKI (Russel, 2000). In our study, patients who developed AKI, even the minor forms, had CK values > 12,800 U/L.

Other tests show hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia, together with increased values for other muscle enzymes, such as lactic-dehydrogenase (LDH), aldolase, aminotransferases and carbonic anhydrase III. Both AKI and increased release of

creatinine from skeletal muscles lead to an increased concentration of creatinine and blood urea nitrogen (BUN), with a decrease of BUN/creatinine ratio from 10:1 to 6:1, or less (Russel, 2000). In our study, we noticed increased levels of BUN, creatinine, uric acid, and metabolic acidosis in patients who developed AKI, and the dyselectrolytemia frequently recorded consisted of hyperkalemia and hypocalcemia, which were corrected with conservative treatment, without the need of hemodialysis. Coagulation tests might show DIC associated with rhabdomyolysis, and toxicological tests will show the drugs or toxins involved (Schwartz et al., 1989). Toxicological tests in patients with drug overdoses were positive for the offending agents involved. The urine examination shows proteinuria, pigmented cast, uric acid crystals, and electrolyte changes suggestive of AKI (Sinert et al., 1994).

The early systemic complications include hyperkalemia, hypocalcemia, arrhythmias, cardiac arrest and hepatic injury (25%), explained by the release of muscle proteases. The late systemic complications are AKI (15%) and DIC, in 12-72 hours after the acute muscle injury (Poels & Gabreels, 1995; Hoogwerf et al., 1979). Early, or late, local complications might occur: the compartment syndrome (when muscle groups with limited expansion by tight fascia are affected) and compression paralysis (Poels & Gabreels, 1995). A delay bigger than 6 hours in this complication diagnosis might lead to irreversible muscle damage or even death. Decompressive fasciotomy is taken into consideration when compartment pressure increases more than 30 mmHg (Schwartz et al., 1989). In our study, the early complications recorded were dyselectrolytemia (43.75%), liver damage (25%). The late complications were severe AKI (12.5%), and nerve paralysis (one patient).

Medical management of rhabdomyolysis concerns the maintenance of the vital functions. It is important to prevent any further damage from the muscle breakdown. In addition, prevention and treatment of renal failure are crucial because it is the most common complication of this phenomenon (Table III.2). Hydration is the basis of treatment (Lionte et al., 2009; Coco & Klasner, 2004). Normal saline should be given intravenously at a rate that maintains urine output at 1 mL/kg per hour or more. Fluid therapy will enhance the excretion of toxic substances that may damage the kidneys. If renal failure is significant despite fluid therapy, renal dialysis may be considered. Frequent monitoring and correction of any serum electrolyte imbalances such as hyperkalemia are also recommended. Hyperkalemia may lead to a life-threatening arrhythmia, so continuous cardiac monitoring and frequent ECGs are indicated (Camp, 2009; Guis et al., 2005).

Retrospective studies showed the benefit of early massive hydration to reduce the risk for AKI. Aggressive hydration increases glomerular filtration rate, improved oxygen delivery to renal tubules and dilutes the toxins. Forced diuresis started the first six hours after admission decreased the incidence of AKI (Zarger, 1996; Gronert 2001). Despite the therapy administered, some patients frequently develop acute oliguric tubular necrosis, when daily hemodialysis is indicated. In time, the renal function is recovered, especially when there is no antecedent renal pathology (Poels & Gabreels, 1995). Skeletal muscle recovers with minimal permanent sequelae after a rhabdomyolysis episode. The rate of survival in rhabdomyolysis is over 77%, and in case of intensive care, including hemodialysis, the majority of deaths are caused by the comorbidities of the patient, not a direct cause related with rhabdomyolysis (Criddle, 2003; Honda, 1983; Stein, 1978).

The patients included in our study received the therapies mentioned in literature, including CVVH (one patient). All survivors of the acute drug overdose complicated with rhabdomyolysis recovered completely the renal function, without any muscle sequelae. The survival rate in our study was 87.5%.

Table III.2. The management of non-traumatic rhabdomyolysis
(adapted from Criddle, 2003; Russel, 2000; Gronert, 2001; Honda, 1983; Zager, 1992)

The purpose	The methods and means
1. Prevention and early detection.	Urinary output and color monitoring. Repeated determination of serum CK.
2. Limiting the further muscle damage.	Reduced immobilization in reclining position. Unloose of tight clothes. Compartment syndrome monitoring. Fasciotomy, cleaning and surgery for wounds and bedsores. When needed, antidote, antivenom and antibiotic administration.
3. Increasing the toxin clearance to minimize the risk for AKI and obtaining an urinary output of 300 mL/h until the myoglobinuria resolves, then an urinary output of >150 mL/h until CK decrease < 1000 U/L	Insert a urinary catheter Administer isotonic crystalloids Administer albumin Urine alkalinization (pH >6) 100 ml 25% mannitol solution in 15 minutes with furosemide 40-120 mg IV Furosemide 200 mg in 2 hours, if no response to mannitol Monitoring of administered fluids, hourly diuresis, daily weighting, clinical examination (jugular veins distension, edema, lung auscultation) to detect hyperhydration or the onset of AKI Hemodialysis Continuous veno-venous hemofiltration and dialysis (CVVH) Swan Ganz catheter to monitor capillary wedged pressure, which reflect accurate the volume status.
4. Prevent the myoglobin breakdown into its nephrotoxic metabolites (ferrihemate)	Urine alkalinization with bicarbonate Loop diuretics Obtaining and maintaining urinary pH >6-6.5 and plasma pH to 7.40-7.45
5. Dyselectrolytemia correction	
• Hyperkalemia	Early administration of Kayexalate p.o. (30-60 g in 20% sorbitol if the intestine is functional) IV hypertonic glucose and insulin administration (in 5 minutes) when K^+> 6.5 mEq/L
• Hyperphosphatemia and hypocalcemia	Administer IV calcium to ameliorate cardiac toxicity (hemodynamic instability and arrhythmias), if present (10% 5-10 mL in 2 minutes). Oral administration of calcium carbonate or hydroxide to correct hyperphosphatemia. Calcium salts are recommended only in case of suggestive ECG changes for hypocalcemia and hyperkalemia, or manifest tetany.
6. Complications management in case of lack of response to conventional therapies	Daily hemodialysis CVVH Peritoneal dialysis (rarely indicated – too slow)
7. DIC treatment (in case of massive bleeding)	Fresh frozen plasma administration Heparin
8. Antioxidant therapy to limit the free oxygen radical formation	Pentoxiphylline with anti-inflammatory, antioxidant, and antifibrotic effects (enhances microcirculation, decreases the neutrophils adhesion and cytokine release). Vitamins E, C, minerals (Zn, Mn, Se) – with antioxidant activity.

The main cause of death in non-survivors was multiple organ failure, and respectively acute fulminant liver failure (secondary to acute chloroform, acetone and ethanol poisoning), with DIC. Non-survivors were addicted to alcohol and had associated comorbidities. Although rare, rhabdomyolysis is a serious and potentially life-threatening complication of TMP-SMX treatment. Trimethoprim-sulfamethoxazole is a popular, effective and inexpensive drug, which is associated with a range of adverse effects, some with fatal outcomes. The exact mechanisms for some of the adverse effects of TMP-SMX have not been defined yet. In addition, more studies are needed to understand the influence of pharmacokinetics on the metabolism of other

drugs and their interactions, such as NSAIDs and TMP-SMX in this case. Clinicians should be aware of the potential consequences when prescribing TMP-SMX. They should educate the patients about correct dosage, possible drug interactions, and adverse effects of the therapy.

Conclusions

Non-traumatic rhabdomyolysis is a potentially lethal syndrome, with a wide spectrum of clinical and paraclinical manifestations, which we documented in 16,7% patients with an altered mental status admitted in an Internal Medicine Department. Clinical presentation ranges from myalgia and severe muscle weakness to symptoms which suggest the involvement of other organs and systems, which strictly requires a comprehensive differential diagnosis, especially in obtunded or agitated patients. Alcoholism, drugs in therapeutic dose or overdose, toxins, strenuous exertion, seizures, prolonged immobilization in certain positions are the common causes of non-traumatic rhabdomyolysis. The diagnosis is confirmed by the CK levels. AKI and dyselectrolytemia (which is responsible for arrhythmias) are the major complications. With a correct therapy, the outcome is good, without permanent muscle damage, and a survival rate over 80%.

III.1.2. Cardio-vascular disorders after acute drug exposure

This direction of research is reflected in the following published articles:

1. Bologa, C; Ciuhodaru, L; Coman, A; Petris, O; Sorodoc, L; **Lionte C.** Unusual cause of spontaneous unilateral intracerebral hematoma-acute methanol poisoning: case report. *Am J Emerg Med* 2014; 32(9): 1154.e1–1154.e2.doi:10.1016/j.ajem.2014.02.034 (**FI 1.274**)
2. Sorodoc V, Petris O, Jaba IM, Bologa C, Sorodoc L, **Lionte, C.** Cardiovascular disorders in acute drug intoxications: six years experience of a tertiary poison center from Romania. *Romanian Medical Journal* 2014; 61(3): 205-210. (ISSN: 1220-5478) EBSCOhost Academic Search Complete. Accession Number: 99715676
3. Puha G, **Lionte C (correspondent author),** Bologa C, Sorodoc L. An unusual cause of myocardial ischemia in young adults. *Rom J Cardiol* 2016; 26 (4): 471-475. (ISSN – print: 1220-658X). EBSCO-host Academic Search Complete. Accession Number: 120087848
4. Sorodoc V, Sorodoc L, **Lionte C**, Gazzi E, Jaba IM, Mungiu OC. Intentional poisoning with ACE inhibitors. Emergeny Hospital Iaşi. *Rev Med Chir Soc Med Nat Iasi.* 2010;114(2):359-62. (ISSN: 0048-7848) PMID: 20700967
5. **Lionte C.** Toxic and drug-induced syncope in medical practice. *Therapeutics, Pharmacology & Clinical Toxicology*. 2009; 13(4): 400-408. (ISSN 1583-0012) EBSCOhost Academic Search Complete. Accession Number: 60002463
6. Şorodoc L, **Lionte C,** Laba V, Solovăstru L. Therapeutical particularities of dysrhythmias in tricyclic antidepressant poisoning. *Archives of the Balkan Medical Union*, 2004; 39(4): 299-303. (ISSN: 0041-6940).

Background

Acute poisonings continue to represent an important cause of morbidity and mortality all around the world. According to the American Association of Poison Control Centers (AAPCC), drugs have the biggest incidence among poisonings, followed by household products (Bronstein et al., 2008). When occurring in acute poisonings, cardiovascular complications, especially dysrhythmias, lead to poor outcomes, even death (Hoffman et al., 2007). In the past, case reports and case series were the studies most commonly published in this respect. The lack of epidemiological information regarding rhythm and conduction disturbances in acute drug poisonings determined us to conduct this study.

Aim of the research

Our aim was to analyze the pattern of dysrhythmias and arterial blood pressure changes occurring in acute drug poisonings and to compare these data with similar reports from literature. The study was performed on 695 cases of acute drug poisonings, admitted at the Internal Medicine Toxicology Clinic of Emergency Clinical Hospital Iasi, the place where all the poisoned patients from Iasi County are referred. It represents the tertiary center for Clinical Toxicology in the North-Eastern region of Romania.

Materials and methods

A retrospective analysis of medical records was performed for all 695 patients admitted with acute drug poisonings in The Toxicology Clinic of the Emergency Clinical Hospital Iasi, Romania, in the previous six years. The cases were selected based on the patient's diagnosis on discharge, by analyzing the medical records of all hospitalized patients. The charts were abstracted by physicians participating in the study using a standardized data collection form, in a Microsoft Excel spreadsheet. The demographical data (age, gender) were collected, as well as additional parameters such as: drug category, clinical form of poisoning (mild, moderate, and coma), declared alcohol intake and blood alcohol levels. The values of the blood pressure were recorded and an analysis of the recordings of electrocardiographic changes in all patients in the first 6 hours was also performed. Electrocardiographic disturbances, hypo- or hypertension recorded before the actual hospitalization or declared by the patient, relatives or supported by previous medical documents, were not included. Drugs were classified as benzodiazepines, barbiturates, neuroleptics, anticonvulsants, antidepressants, cardiovascular drugs, acetaminophen, NSAIDs and nonopioid analgesics, antibiotics, hypoglycemic agents, opioids, tuberculostatic, other medication (vitamins, antithyroid drugs, iron compounds, etc.) and unknown drugs. First, the blood pressure changes were quantified and the patients were classified in three categories: normal blood pressure, hypertension (>140/90 mmHg in accordance with The European Society of Hypertension Guide 2013) and hypotension (<90/60 mmHg) (Mancia et al., 2009). Depending on the heart rate, patients were divided in three categories: normal heart rate, tachycardia and bradycardia. Electrical changes were analyzed and grouped in the following categories: normal electrocardiogram, premature beats, ischemic changes, conduction disturbances, supraventricular arrhythmias, long QT interval, ventricular arrhythmias. For the accuracy of the study, two teams of abstractors revised all the data, including the electrocardiogram. Inter-rater reliability was calculated by using 36 (6 per year) medical charts. All abstractors reviewed the entire set of randomly selected medical charts. Inter-rater agreement was assessed by using κ analysis. The database was statistically analyzed using SPSS for Windows 16.0. The chi-square test for comparing nominal variables was used when proportions were analyzed for significant differences (Jaba et al., 2010). Differences were considered statistically significant when p values were under 0.05.

Results.

For the given period of six years, 2,556 cases of acute poisonings were recorded and drug poisonings made up 27.19% (695 cases). The blood pressure was normal in 79.3% of patients, hypertension was encountered in 6.6% and in 14.1% of the patients, hypotension was observed. From the total number of hypertension cases, 32.92% of patients ingested more than one drug, 8.51% were barbiturates poisonings, 8.63% anticonvulsants and 8.7% were analgesics (nonopioid and opioid) poisoning (p 0.000) (Figure III.4).

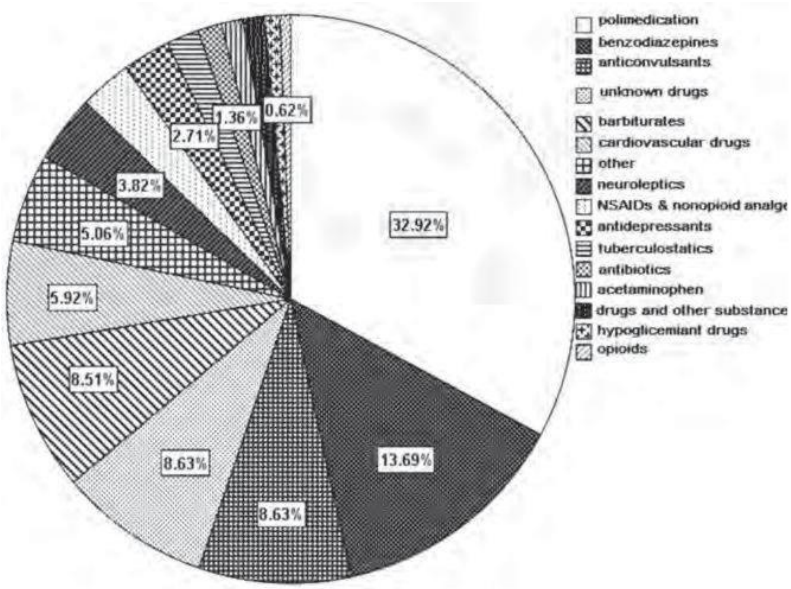


Figure III.4. Prevalence of drug poisoning recorded during the study

Out of the total cases of hypotension, 41.8% were encountered in combined drug poisonings, 18.4% in cardiovascular drug poisonings and 16.3% in barbiturates poisonings ($p < 0.001$) (Figure III.5).

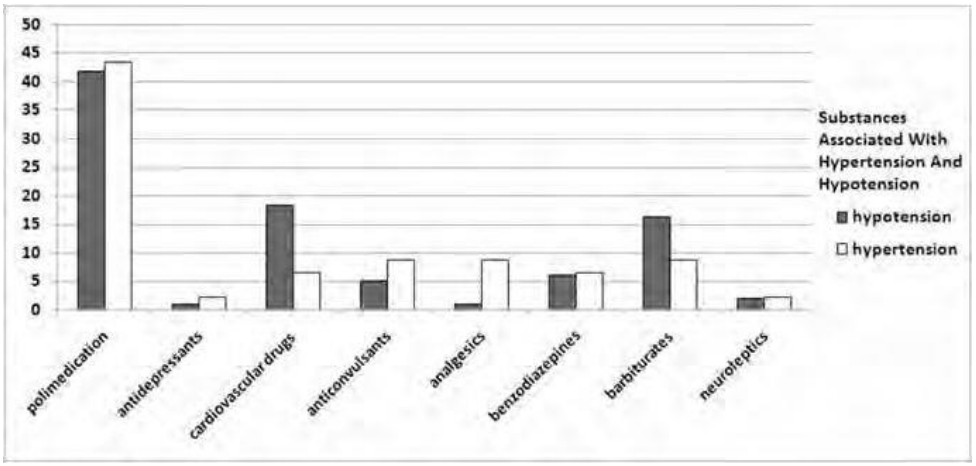


Figure III.5. Substances associated with hypertension and hypotension

Analyzing the drug category responsible for the poisoning, we observed that hypotension occurred in a significant percent in cardiovascular drugs (48.6%) and barbiturates poisonings (25.8%) (Table III.3).

In women, we registered 25 cases of hypertension and in men 21 cases. Hypotension occurred more frequently in women (67 cases) than men (31 cases) ($p < 0.001$). The highest number of hypertension cases was observed in patients aged 41-50 years, while hypotension was more frequent in the 21-30 age group ($p < 0.001$). Hypotension was more frequent in patients with concomitant use of alcohol (76.5%) compared with patients without declared alcohol consumption (23.5%) ($p < 0.001$). From the total number of 46 hypertension cases, in 20 cases the blood alcohol level was over 50 mg/dl, in 14 cases it was normal and in 12 cases the alcohol blood exam was not determined. For hypotension (98 cases), 18 cases were

accompanied by blood alcohol level higher than 50 mg/dl, in 46 cases the level was normal and in 34 cases the blood alcohol level was not determined (p 0.01). Both arterial blood pressure changes (hyper- or hypotension) had an increased incidence in moderate and severe clinical forms (coma) when comparing to mild forms ($p < 0.001$).

Table III.3. Characteristics of blood pressure and heart rate considering the drug category inducing the poisoning

Category	TOTAL CASES (No.)	BLOOD PRESSURE			HEART RATE		
		NORMAL (%)	HYPER-TENSION (%)	HYPO-TENSION (%)	NORMAL (%)	TACHYCARDIA (%)	BRADYCARDIA (%)
POLIMEDICATION	255	76.1	7.8	16.1	65.9	27.1	7.1
DRUGS AND OTHER SUBSTANCES	10	90.0	-	10.0	60.0	30.0	10.0
BENZODIAZEPINES	96	90.6	3.1	6.3	70.8	24.0	5.2
BARBITURATES	62	67.7	6.5	25.8	59.7	22.6	17.7
ANTIDEPRESSANTS	19	89.5	5.3	5.3	52.6	42.1	5.3
NEUROLEPTICS	25	88.0	4.0	8.0	76.0	24.0	-
CARDIOVASCULAR DRUGS	37	43.2	8.1	48.6	54.1	21.6	24.3
ACETHAMINOPHEN	10	90.0	10.0	-	80.0	10.0	10.0
ANTICONVULSANTS	56	83.9	7.1	8.9	64.3	28.6	7.1
NSAIDs and NONOPIOID ANALGESICS	20	75.0	20.0	5.0	70.0	25.0	5.0
ANTIBIOTICS	5	100.0	-	-	80.0	20.0	0
HIYPOGLYCEMIC AGENTS	5	100.0	-	-	100.0	-	-
OPIOIDS	2	50.0	-	50.0	50.0	50.0	-
TUBERCULOSTATICS	14	85.7	-	14.3	64.3	28.6	7.1
OTHERS	29	96.6	3.4	-	55.2	41.4	3.4
UNKNOWN DRUGS	50	84.0	8.0	8.0	64.0	26.0	10.0
TOTAL	**695**						

The heart rate had normal values in 65.2% of the patients, tachycardia in 26.5% and in 8.3% of cases bradycardia was encountered. For heart rate disturbances there were no statistically significant differences between age and gender groups. Out of the total number of tachycardia cases, 36.8% were associated with combined drug poisonings, 12.6% with benzodiazepines poisonings, followed by anticonvulsants (8.2%) and barbiturates poisonings (7.7%). Bradycardia was encountered in 30.4% of the cases in combined drug poisonings, 17.9% in barbiturates, 16.1% in cardiovascular drugs and 8.9% in benzodiazepine poisoning cases.

In relation with drug category, we noticed that from the total number of benzodiazepine poisonings, 24% had tachycardia, the same situation (around 25% of the total number of patients) being encountered in neuroleptics, anticonvulsants, NSAIDs, non-opioid analgesics and tuberculostatic drugs. Tachycardia was found in an important percent (42.1%) of all the antidepressants poisoning cases and in 17.7% of the barbiturate poisonings (Table III.3). The incidence of tachycardia and bradycardia was almost the same in clinical forms of moderate severity or those in coma when compared to mild forms: 62 cases of tachycardia and 21 cases of bradycardia in mild forms, 52 cases of tachycardia and 23 cases of bradycardia in moderate forms and 68 cases of tachycardia and 12 cases of bradycardia in coma situations ($p < 0.001$). Tachycardia was more frequent in patients with declared alcohol intake (p 0.004). In six of the cases of bradycardia, the blood alcohol levels were between 50-300 mg/dl, in 25 cases the levels were normal and in 25 cases these tests were not demanded. For the majority of the tachycardia cases (76 cases) the blood alcohol levels were normal, in 48 cases the levels were between 50 and 300 mg/dl and in 58 cases testing were not recommended. The distribution of

combinations between heart rate disturbances and arterial blood pressure changes are illustrated in Table III.4. The differences were statistically significant ($p < 0.001$).

Table III.4. The distribution of combinations between heart rate disturbances and arterial blood pressure changes

HEART RATE	ARTERIAL BLOOD PRESURE			Total
	Normal	Hypertension	Hypotension	Cases no
Normal	393	21	39	453
Tachycardia	129	22	33	184
Bradycardia	29	3	26	58
Total	551	46	98	695

Electrocardiogram, being a routine test, was performed in all patients with acute drug poisonings. Normal aspects of electrocardiogram were recorded in 85.2% of patients, and only 14.8% of the patients had rhythm and conduction disturbances other than tachycardia or bradycardia. The most frequent finding on electrocardiogram was ischemia (40 cases) followed by conduction disturbances (35 cases) (Table III.5). Supraventricular disturbances were a rarely encountered condition, found in only 12 cases, and just one case of ventricular arrhythmia was observed (ventricular tachycardia). The biggest number of abnormal electrocardiograms was found in cardio-vascular drug poisonings (12 cases) and benzodiazepine poisonings (9 cases) (p 0.003).

Table III.5. Electrocardiogram recordings in acute drug poisonings in relation with drug category

CATEGORY	Normal EKG	Premature beats	Ischemia	Conduction disturbances	SVD	VD	LONG QT
POLIMEDICATION	204	3	22	18	6	1	1
DRUGS AND OTHER SUBSTANCES	9	-	-	1	-	-	-
BENZODIAZEPINES	87	-	5	3	-	-	1
BARBITURATES	55	-	3	2	1	-	1
ANTIDEPRESSANTS	18	-	-	1	-	-	-
NEUROLEPTICS	21	-	1	2	1	-	-
CARDIOVASCULAR DRUGS	25	2	4	3	3	-	-
ACETHAMINOPHEN	10	-	-	-	-	-	-
ANTICONVULSANTS	50	1	3	2	-	-	-
NSAIDs and NONOPIOID ANALGESICS	19	-	-	-	-	-	1
ANTIBIOTICS	4	-	-	1	-	-	-
HYPOGLYCEMIC AGENTS	5	-	-	-	-	-	-
OPIOIDS	2	-	-	-	-	-	-
TUBERCULOSTATICS	14	-	-	-	-	-	-
OTHERS	28	-	-	1	-	-	-
UNKNOWN DRUGS	43	3	2	1	1	-	-
TOTAL	**594**	**9**	**40**	**35**	**12**	**1**	**4**

EKG – electrocardiogram
SVD – supraventricular disturbances
VD – ventricular disturbances

Patients aged 31-40 had the highest incidence of electrocardiogram disturbances ($p < 0.001$). The clinical forms of moderate severity and those of comatose patients had electrocardiographic abnormalities more often ($p < 0.001$). There were 32 cases of abnormal electrocardiogram in mild forms (8.86%), 33 in moderate forms (16.75%) and 36 cases in comatose states (26.27%). There were no statistically significant differences between cases with declared alcohol intake as compared with cases without alcohol intake for abnormal electrocardiograms. Electrocardiographic disturbances occurred more frequently in cases with tachycardia (38 cases) compared with bradycardia (13 cases) (p 0.02) and in patients with hypotension (p 0.006). No life-threatening dysrhythmias and no deaths were reported due to

cardiac toxic effects in our study. The inter-rater score for categorical variables varied between 0.92 and 1, expressing a good inter-rater reliability.

Discussion and conclusions

This study provides information about the frequency of arterial blood pressure changes and dysrhythmias in acutely drug poisoned patients admitted in the Toxicology Clinic of the Emergency Clinical Hospital Iasi, over a six-year period. This study reflects the current state of matters encountered in a toxicology clinic. In certain cases, some of these disturbances could have been pre-existing and unknown to the patient, and the current poisoning could have aggravated previous dysrhythmias or blood pressure changes. The most important finding of our research was that cardiac toxic effects are rare, hypertension being encountered in 6.6%, hypotension observed in 14.1% of patients, tachycardia documented in 26.5% of patients and bradycardia in 8.3%. Only 14.5 % of patients had rhythm and conduction disturbances, fact reported by other researchers too (Mach et al., 2004). For both arterial blood pressure changes and rate disturbances, combined drug poisoning was the most frequently involved category. Among the intoxications involving single substances, following cardiovascular drugs, barbiturates were the most frequent in the etiology of hypotension.

Tachycardia was most frequently associated with ingestion of antidepressants, benzodiazepines and anticonvulsants. Sinus tachycardia, the most common rhythm disturbance in antidepressants overdose, has a multifactorial etiology, including anticholinergic effects, increased norepinephrine release, and reflex tachycardia (in response to vasodilatation). Tachycardia is recognized to be a sign of significant toxicity in this acute poisoning (Brush & Aaron, 2007). Although antidepressant poisoning is known as a poisoning with important cardiac complications, this wasn't confirmed by our research, possibly due to the limited number of cases. Marketing of newer and safer categories of antidepressants, with less cardio-toxic effects, could also explain our findings. Barbiturates, cardiovascular drugs and benzodiazepine poisoning were mostly involved in the etiology of bradycardia. Barbiturates induce cardio-vascular depression secondary to a negative inotropic effect and sodium channel-blocking action, followed by hypotension and bradycardia (Lynton, 2007). Our results support this toxicological mechanism. Cardiovascular drugs involved in acute poisonings in our study were calcium channel blockers, beta blockers, angiotensin converting enzyme inhibitors, diuretics, nitrates, digitalis, angiotensin II receptor antagonists, antiarrhythmics. Bradycardia in such intoxications has multiple explanations, such as directly interacting with myocardial membranes and receptors or an indirect cardio-depressant effect, altering autonomic output or causing reflex changes in the heart (Patel & Benowitz, 2005). Cardiac toxic effects of benzodiazepines come as the result of reducing the sympathetic tone and increasing the parasympathetic tone. Previous studies have shown that both hypotension and bradycardia are clinical features in this type of poisoning (Farrell & Fatovich, 2007). In our study, benzodiazepines poisonings are accompanied more often by tachycardia, facts cited in severe acute poisonings (Sorodoc, 2005). Tuberculostatic poisonings were accompanied by both hypotension and tachycardia in our study. The proposed mechanism for this might be a decreased catecholamine synthesis (Bowersoxk et al., 1973; Parish &Brownstein, 1986). In the case of poisoning by analgesics, arterial hypertension is cited as result of an increase in hydro-saline retention (Brotman, 2003; Aisen et al., 2003; Curhan & Stampfer, 2003), fact encountered in our study, too.

All the cardiac toxic effects had a significantly increased incidence in the case of moderate clinical forms and coma as opposed to mild forms. The incidence of tachycardia and hypotension increased when alcohol was ingested concomitantly with the drugs involved. It is well known that alcohol co-ingestion aggravates the effects produced by sedative-hypnotics,

antidepressants and cardiovascular drugs. Ethanol itself is responsible for inducing tachycardia and cardiovascular collapse in moderate to severe clinical forms of acute poisoning (Wilson & Waring, 2007).

In conclusion, cardiac toxic effects were not frequent in acute drug poisonings cases admitted in our clinic, associated especially to clinical forms of moderate severity and to cases of coma. No life-threatening situations and no fatalities occurred among our patients. Further studies concerning dysrhythmias, including larger numbers of patients are still necessary.

III.1.3. Metabolic consequences of drug overdose.

This direction of research is reflected in the following published articles:

1. Sorodoc L, **Lionte C,** Sorodoc V, Petris OR, Badiu, C. Causes, morbidity and management of drug-induced hypoglycemic coma in non-diabetic patients**.** *Acta Endocrinologica-Bucharest* 2009; 5(3): 337-348. (ISSN: 1841-0987) DOI 10.4183/aeb.2009.337 **(FI 0.011)**
2. Bologa C, Coman A, **Lionte C**, Petriș O, Șorodoc L. Hyperglycemia and Lactic Acidosis after ingestion of a Lethal Dose of Slow Release Nifedipine – case report. *Journal of US-China Medical Science* 2010; 7(4): 50-53. (ISSN: 1548-6648)
3. **Lionte C,** Șorodoc L, Laba V. Acute pulmonary edema and insulin-induced hypoglycemia in a non-diabetic subject. *Timisoara Medical Journal* 2004; 54(4): 358-361. (ISSN 1583-5251)
4. **Lionte C**, Șorodoc L, Laba V. Toxic-induced hypoglycemia in clinical practice. *Rom J Intern Med* 2004; 42(2): 447-455. (ISSN: 1220-5818). **PMID: 15529635 (11 citations in ISI Web of Knowledge)**

Background

Toxic induced hypoglycemia is usually caused by the anti-diabetic treatment and excessive alcohol consumption. Hypoglycemia in diabetics treated with insulin or anti-diabetic oral agents is by far the most studied form of hypoglycemia. Less information is available on toxic-induced hypoglycemia in non-diabetic subjects with acute exogenous poisoning.

Hypoglycemia, a syndrome characterized by adrenergic and neuroglycopenic symptoms induced by an abnormal level of plasma glucose (glycemia < 50 mg/dl), is a common, potentially fatal, yet preventable problem. While hospital admission as a medical emergency to treat hypoglycemic coma appears to be infrequent and is not confined to people receiving treatment for diabetes, a paucity of information is available on causes and outcome of such episodes in non-diabetics. Patients may present with autonomic symptoms (e.g., sweating, hunger, paresthesia, tremor, palpitation, and anxiety), neuroglycopenic symptoms (e.g., dizziness, weakness, confusion, drowsiness, seizure, and coma), which may lead to death if unrecognized and untreated (Cryer, 1999). To address this issue, we performed a retrospective study of identified drug-induced hypoglycemic coma (DIHC) that had determined admission to a regional emergency hospital in an urban center, over a period of 18 years.

We also performed a prospective study in those poisonings associated with hypoglycemic risk, to assess the prevalence of toxic-induced hypoglycemia.

Patients and methods

We retrospectively analyzed 18,642 non-diabetic patients suffering from drug overdose, admitted in the Medical Clinic of "Sf. Ioan" Emergency Clinic Hospital Iasi from January 1991 until December 2008. For this purpose, we searched the hospital medical records

system, for selected codes from the International Classification of Diseases, that had been applied to the diagnoses listed in discharge summaries in the period mentioned. We identified 79 patients with DIHC. We also analyzed medical records of patients admitted in an intensive care unit (ICU) of our hospital, as well as the records of the Emergency Room (ER), to identify any cases that could have been coded incorrectly. The case records of patients who had been recorded as having hypoglycemic coma were examined to confirm that the hospital admission was precipitated by hypoglycemia, to assess the clinical manifestations and the cause of hypoglycemic coma. Measurement of a low blood glucose provided evidence for hypoglycemia. Blood and urine were collected from all the patients for toxicological analysis.

Our prospective study was performed in the span of one year on 1,034 non-diabetic patients admitted in Emergency Clinic Hospital Iasi, with a diagnosis of acute poisoning. Selection criteria were: type of toxin - ethanol, beta-blockers, salicylates, wild mushrooms. Exclusion criteria were: hypoglycemia caused by another factor than poison itself (endocrine-related, functional, early diabetes); patients who did not cooperate or accept the biochemical and toxicological assessment: another disease, more severe than the acute poisoning, which determined evaluation and treatment of the patient in another department (acute coronary syndrome, neurological, trauma or surgical disease). For each subject enrolled in the prospective study we performed biochemical and toxicological tests, including a 6-hour oral glucose tolerance test (OGTT) in the admission day, imaging studies (abdominal ultrasonography) and histopathological examination in patients who deceased. All continuous variables were expressed as mean ± standard deviation. Variables were analyzed with unpaired Student's t test (to compare mean values and percentages) and χ^2 test to assess the presence of a significant difference among groups. Significance was taken as a $p < 0.05$.

Results

From January 1991 to December 2008, we identified 18,642 admissions in non-diabetic patients diagnosed with acute poisoning, of which 10,029 were acute drug intoxications (with a single agent or multiple agents, including a drug and a toxin, such as ethanol). We identified 5,383 cases with acute intoxication which had a hypoglycemic potential, 2,153 of these being acute intoxication with ethanol alone. Of 3,230 patients with acute drug intoxication which have a hypoglycemic potential, we identified 80 admissions with DIHC in suicide attempt of 79 patients, representing 0.78% of acute drug intoxications in suicide attempt and 2.44% of drug intoxications with hypoglycemic risk. One of these patients was admitted twice in the same year, once with insulin-induced hypoglycemic coma, and the second time with DIHC caused by overdose with a beta-blocker with an oral hypoglycemic agent (OHA).

The poisonings most frequently associated with hypoglycemic risk were, in our study, alcohol acute poisoning (40%), wild mushroom poisoning (29%), beta-blocker poisoning (23%), salicylate poisoning (7%) and finally acute poisoning with anti-diabetic agents such as insulin and oral anti-diabetic agents (1%) - Figure III.6.

Of 79 patients with DIHC, insulin was self-administered in 38 patients (48.10%), intoxications with OHA were found in 34 cases (43.04%), 5 patients (6.33%) experienced hypoglycemic coma after attempting suicide using beta-blockers, and 2 patients (2.53%) had hypoglycemic coma induced by acetylsalicylic acid associated with alcohol.

Acute poisoning with hypoglycemic risk occurs rarely in patients aged over 50 years (<10% cases). There was an increased number of poisonings among people who lived in urban regions (63.87%), compared with people from rural regions (36.13%), because of the easier access to diverse drugs and toxins and of a high percentage of alcoholism in urban zones.

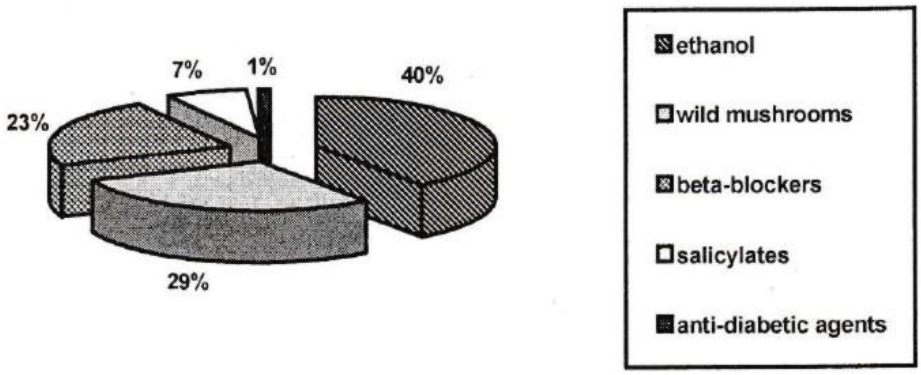


Figure III.6. Prevalence of poisoning with hypoglycemic risk

Of 79 patients with DIHC, 48 (60.76%) were women, aged 38.92 ± 19.19, and 31 (39.24%) were men, aged 32.71 ± 16.33. The dose of self-injected insulin was between 400 and 750 IU. The causative OHAs are presented in Fig. III.7. Beta-blockers involved were propranolol (in 3 cases, ingested doses between 1.2 - 1.8 g), and metoprolol (2 patients).

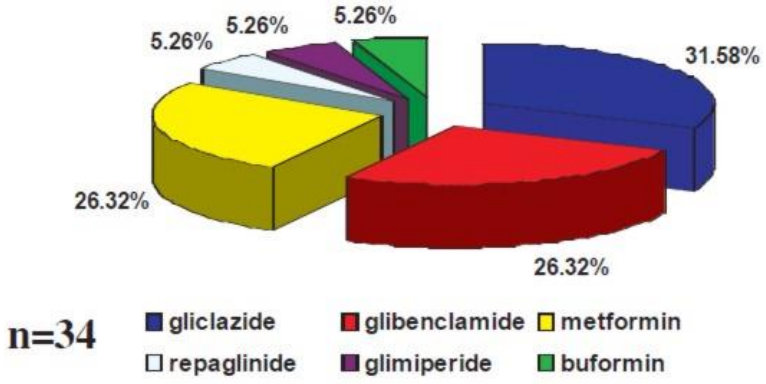


Figure III.7. Oral hypoglycemic agents involved in DIHC

Eleven cases were intoxications with several drugs (one of which with hypoglycemic potential), as follows: association of 2 OHAs (gliclazide and metformin) - 1 patient, combination of a beta-blocker with digoxin, and ACE inhibitor - 1 patient, association of OHA with diltiazem - 1 case, OHA and nifedipine - 1 case, OHA and tricyclic antidepressants - 1 case, OHA and propranolol - 1 case, OHA and amiodarone - 1 patient, and 4 cases had association of an OHA and over-the-counter medications. In 4 cases ethanol was involved (2 salicylates intoxication, and 2 insulin), but the dose of alcohol could not explain the coma or the severity of hypoglycemia, blood alcohol level being 45 ± 8 g/L. Associated medical conditions in our patients were: chronic alcoholism - 2 cases, hypertension - 3 patients, chronic heart failure - 1 case, depression - 8 patients, of which 7 cases with previous suicide attempts using other drugs, dementia - 2 cases, personality disorder - 5 cases. Regular medications in our patients were: diuretics - 2 cases, calcium channel-blockers - 1 patient, beta-blockers - 1 case, antiarrhythmics - 1 patient, antidepressant or antipsychotic medication - 2 cases.

All 79 patients with DIHC were admitted to the hospital because of loss of consciousness, 15 of them (19%) having also generalized seizures on admission. GCS was

below 8 in all patients (ranged from 3 to 7); 2 patients (2.53%) suffered transient focal neurological disturbances during hypoglycemia. Autonomic symptoms (sweating, tachycardia) were present on admission in 28 patients (35.44%). Diagnostic difficulties were noticed in patients with coma and seizures. In these cases, several tests to confirm hypoglycemia as the only cause of this association were performed. Many patients had been suspected of having hypoglycemic coma, and had been given IV Glucose before the blood glucose was measured in hospital. The blood glucose recorded on admission was variable, and ranged from 12 to 52 mg/dl, with a median value of 29.14 mg/dl. C-peptide measurement and serum insulin were not available. Liver and renal function tests, toxicological screen and studies considered to rule out the possibility of a concurrent occult infection contributing to the hypoglycemic episode were performed (chest radiograph, urinalysis, and blood cultures).

In this prospective study, analysis regarding patients with acute ethanol poisoning showed that hypoglycemia was present at glucose level determination in 26.36% cases assisted in emergency room (ER). Based on 6 hours OGTT, we found hypoglycemia in 30% cases admitted in the medical clinic with moderate-severe form of alcohol intoxication. Intoxication with wild mushrooms was complicated with hypoglycemia only in forms with delayed onset of symptoms (>6 hours from ingestion) caused by cyclopeptide containing species, especially Amanita phalloides. We found 7 patients with phalloidian syndrome complicated with acute liver failure and in 5 out of 7 patients, hypoglycemia was present. Six out of 7 patients with phalloidian syndrome died as a consequence of acute liver and renal failure. Hypoglycemia was found in 28.21% patients with beta-blocker poisoning admitted in hospital, based on 6 hours OGTT and in 11.63% cases assisted in ER, based on glucose level determination. Hypoglycemic curves in OGTT were more frequent in patients from rural regions (100%) than in patients from urban regions (51.61%, p 0.01). Salicylate poisoning was responsible for hypoglycemia in 5.55% cases admitted in the medical clinic (based on 6 hours OGTT). Patients with salicylate intoxication assisted in the ER had normal blood glucose levels.

We performed an analysis of all types of poisoning associated with hypoglycemia, with or without liver involvement. Comparing the frequencies of OGTT curves (normal, flat, pre-diabetic, diabetic, reactive hypoglycemia, flat hypoglycemia) in different decades of age, we found that hypoglycemic curves significantly frequent (41.67%) in patients aged 16 to 25, compared with patients aged 36 to 45 (7.69%, p 0.02). In patients assisted only in ER, after determining blood glucose levels, we found that hypoglycemia is frequent (100%) in patients over 65 years old, compared with patients aged 16-25 (9.68%, $p < 0.001$), 26-35 (40.58%, p 0.005), 36-45 (23.29%, p 0.002), 46-55 (42.62%, p 0.008), and 56-65 (32.26%, p 0.003). When we compared blood glucose levels recorded in all patients enrolled in the study, we found that frequency of normal blood glucose (53.43%, $p < 0.001$) and of hyperglycemia (15.20%, p 0.01) appeared significantly higher in patients from urban regions, while frequency of hypoglycemia was higher in patients from rural zones (86.67%, $p < 0.001$). Chronic alcoholism was significantly more frequent associated with hypoglycemic curves in OGTT (40.62%), compared with normal curves in OGTT (22.13%, p 0.04). Referring to patients assisted in ER, in which we determined blood glucose levels, chronic alcoholism was also frequently associated with hypoglycemia (80%) comparatively with normal glycemia (25.17%, $p < 0.001$) and hyperglycemia (27.91%, $p < 0.001$). We compared the frequency of hypoglycemia recorded in all patients with different types of poisoning (after summation the frequency of hypoglycemic curves in OGTT, and hypoglycemia in blood glucose determination). We found that hypoglycemia was significantly more frequent in cases admitted for acute ethanol poisoning (30%), beta-blocker poisoning (28.21%) and in patients with ethanol poisoning assisted in ER (26.36%), compared with patients with beta-blocker poisoning assisted in the ER (11.63%, p 0.02) and patients with toxic mushrooms poisoning (8.20%, p 0.002). We

analyzed the frequency of hypoglycemia in certain types of poisoning, no matter how the patient was managed (admitted in medical clinic or assisted in ER). We found that hypoglycemia is significantly present in ethanol poisoning (28.82%) and beta-blocker poisoning (22.13%), comparatively with salicylate poisoning (5.55%, p 0.01, respectively 0.05) or toxic mushroom poisoning (8.2%, $p < 0.001$, respectively 0.01).

We used, for the first time in our study, standard 6-hour OGTT to assess toxic-induced hypoglycemia in non-diabetic subjects with acute poisoning. Some patients had flat hypoglycemic and reactive hypoglycemic curves in 6-hour OGTT, especially those with alcohol poisoning. Particularly in those patients, a close surveillance for 3-5 hours after admission is needed in order to detect hypoglycemia.

When the initial treatment of hypoglycemic coma was given before admission to hospital, medical/paramedical staff of the ambulance team, or staff in the hospital's ER had administered this in 13 patients (16.45%); 63 patients were treated with an IV bolus injection of 33% glucose, followed by an IV infusion of 5-10% glucose. In 12 patients with DIHC, initial treatment was with glucose bolus injection, and after that further bolus doses were required, while 4 patients initially received advanced cardiac life support, together with IV infusion of glucose. Glucagon was used in beta-blocker poisoning (5 cases), where it has an antidotal effect and reverses hypoglycemia, and also in sulfonylurea-induced hypoglycemia in 10 patients. Benzodiazepines were used to control seizures in 15 patients. Octreotide was used in refractory OHA-induced hypoglycemia in 6 patients.

In the prospective study, 6 of 409 patients with acute poisoning and hypoglycemic risk died (l .46%). Factors which contributed to this outcome in the prospective study were: delayed presentation to the hospital, association of toxins with cumulative effects, cardiac complication (ventricular arrhythmias, asystole as a consequence of hypoglycemia or drug itself), liver failure (responsible for terminal hypoglycemia in patients with mushroom poisoning), renal failure and age >65 years.

Following admission to hospital with DIHC, 12 patients (15.19%) were further treated for hypoglycemia. Two elderly patients had transient focal neurological disturbances during hypoglycemia, with no permanent sequelae. One case (1.26%) with insulin-induced hypoglycemic coma had an episode of acute pulmonary edema following seizures, and recovered completely. Seven patients (8.86%) experienced arrhythmias as follows: 1 woman - paroxysmal atrial fibrillation, 1 woman - transient coronary sinus rhythm, 1 man - ventricular tachycardia (torsade des pointes), with subsequent ventricular fibrillation and death, 1 woman - idioventricular rhythm followed by asystole irresponsive to resuscitation, 3 patients with atrial and ventricular extrasystoles which did not require a specific treatment. The remaining 77 patients (97.47%) recovered without sequelae following hypoglycemic coma. Two cases deceased: a 28-year-old male with attempted suicide using OHA and tricyclic antidepressants, complicated with long QTc interval and torsade des pointes, which finally led to death, and a 23-year-old woman with acute propranolol poisoning in lethal dose, presenting with profound hypoglycemic coma who developed asystole unresponsive to resuscitation maneuvers shortly after admission. Mortality in DIHC in non-diabetic patients was 2.53% in our study.

Discussion

The brain is vitally dependent on glucose for its normal function and is neither able to store nor to synthesize glucose. Depletion of the supply of glucose to the brain rapidly causes impaired neuronal function, manifested by cognitive impairment or depression of level of consciousness, exhibited as obtundation, stupor or coma. When the plasma glucose level declines below 50 mg/dL (2.77 mmol/L), appetite is increased and counterregulatory hormones are released, initially glucagon (the most important hormone for prompt recovery from acute

hypoglycemia) and epinephrine, and later cortisol, growth hormone, and norepinephrine causing glycogenolysis, gluconeogenesis, lipolysis, ketogenesis, and proteolysis (Cryer, 2007; Ben-Ami et al., 1999).

The etiology of hypoglycemia in clinical practice is variable, and includes: drugs, insulinoma, liver failure, renal failure, hormonal deficiencies and reactive hypoglycemia (Service, 1995; Ching et al., 2006). Drugs that may be related to hypoglycemia include the following: oral hypoglycemics, sulfonamide, phenylbutazone, insulin, bishydroxycoumarin, salicylates, p-aminobenzoic acid, propoxyphene, haloperidol, stanozolol, ethanol, hypoglycin, carbamate insecticide, disopyramide, isoniazid, methanol, methotrexate, pentamidine, sulfonamide, tricyclic antidepressants, cytotoxic agents, organophosphates, propranolol plus ethanol, didanosine, chlorpromazine, quinine, sulfa drugs, fluoxetine, sertraline, fenfluramine, trimethoprim, 6-mercaptopurine, thiazide diuretics, thioglycolate, tremetol, ritodrine, disodium ethylenediaminetetraacetic acid (EDTA), clofibrate, angiotensin converting enzyme (ACE) inhibitors, and lithium (Lionte, 2004).

The common causes of acute hypoglycemia are related to diabetes therapy and to the excessive consumption of alcohol, particularly when associated with fasting (Hart & Frier, 1998). Severe hypoglycemia, defined as that associated with coma or requiring assistance of another person for reversal occurs at least once a year in 10% of patients treated with insulin, with a mortality of 2-4% (Casparie & Elving, 1985; Cryer et al., 2003). While it is difficult to assess the absolute rates, the frequency of iatrogenic hypoglycemia is substantially lower in type 2 than in type 1 diabetes. Thus, the rates of severe hypoglycemia in type 2 diabetes are roughly 10% of those in type 1 diabetes even during aggressive therapy with insulin, and deaths caused by sulfonylurea-induced hypoglycemia have been documented (Cryer et al., 2003). A report that assessed hypoglycemia in type 2 diabetes found a 20% incidence of hypoglycemia in sulfonylurea-treated patients (Heller, 2008).

Severe hypoglycemia occurrence and possible etiology in non-diabetics is less well described. Some prospective studies carried out in last decade find that hypoglycemia is present in 12% patients with beta-blocker poisoning and in 30.9% patients with salicylate poisoning, when doses of ingested salicylates are above 20 g, and a 6-h prolonged OGTT is used to assess it (Lionte et al., 2002; Lionte et al., 2003). Among toxic-induced hypoglycemia in non-diabetic subjects, alcohol represents the most frequent cause (28.82%), followed by beta-blockers - 8.2%, and salicylates - 5.55% (Lionte et al., 2003). Attempted suicide with anti-diabetic agents in non-diabetic subjects produced the most severe and prolonged form of hypoglycemia in acute poisoning (Lionte et al., 2004). In a review of 1,418 reported cases of drug-induced hypoglycemia, sulfonylureas (especially chlorpropamide and glyburide), either alone or with a second hypoglycemic or potentiating agent, still account for 63% of all cases; that alcohol, propranolol, and salicylate, either alone or with another hypoglycemic drug, are the next most frequent offenders (19% of the total); quinine, pentamidine, ritodrine, and disopyramide have caused an additional 7% of all episodes of severe hypoglycemia (Seltzer, 1989). A study carried out over 9 years in a Philadelphia teaching hospital identified 88 patients without diabetes who presented with hypoglycemia requiring admission. Common causes included renal failure (25%), alcohol poisoning (15%), liver failure, sepsis, cancer and endocrine disorders (12% each), as well as OHA (3%) (Mendoza et al., 2005). Another study performed in a regional hospital in Hong Kong identified 51 patients without a known history of exposure to OHA, admitted with drug-induced hypoglycemia in a 10-month interval, in which OHAs were documented as underlying cause of hypoglycemia in 45% (Ching et al., 2006). A systematic review on hypoglycemia as a side effect of a drug not used to treat hyperglycemia, showed that the most commonly reported offending drugs were quinolones, pentamidine, quinine, beta-blockers, angiotensin converting enzyme agents, and insulin-like growth factor (Murad et al.,

2009). Although publications documented the occurrence of DIHC, they are referring mainly to diabetic patients (Platia & Hsu, 1979; Ben-Ami et al., 1999).

Our study was addressed only to non-diabetic subjects, in which we find a prevalence of DIHC of 2.44% in situation of acute poisoning with drugs involving a hypoglycemic risk. Anti-diabetic drugs 91.14%, followed by beta-blockers 6.33%, and salicylates 2.53%, represented etiology of DIHC. Drug-induced hypoglycemia continues to be so common that virtually every unconscious patient should be considered hypoglycemic until immediate estimation of the blood sugar level rules it in or out (Seltzer, 1989). Obtaining an accurate medical history may be difficult if the patient's mental status is altered. Physical findings are nonspecific in hypoglycemic coma and generally are related to the central and autonomic nervous systems. According to our results, seizures and focal neurological disturbances may accompany loss of consciousness in 21.51% cases with DIHC. This determines the need for a differential diagnosis with various situations in which coma and convulsions are associated, such as neurological conditions (post-critic coma, brain tumor, rupture of vascular malformation), and other toxic - induced coma (short acting barbiturates, isoniazid, salicylates, non-selective beta-blockers, organo-chlorate pesticides, cocaine) (Lionte et al., 2003; Lionte et al., 2006).

One prospective study of 125 patients seen in the emergency department with symptomatic hypoglycemia showed that coma was present in 32 patients with blood glucose levels of 2-28 mg/dl (Malouf & Brust, 1985). Coma can occur at glucose levels in the range of 41-49 mg/dl (2.3-2.7 mmol/l) as well as at lower glucose levels (Cryer, 2007). In patients with DIHC we found that blood glucose ranged from 12 to 52 mg/dL (mean 29.14 mg/dL). Confirmation of suspected mechanism of hypoglycemia may be sought. Such confirmation might include finding low insulin and C-peptide levels in non-insulin mediated hypoglycemia (Lebowitz & Blumenthal, 1993), such as ethanol hypoglycemia, and blunted plasma glucose responses to intravenous glucagon in hypoglycemia due to abnormal liver function (Service, 1995; Lionte, 2004). Factitious hypoglycemia due to surreptitious insulin administration is usually manifested by erratically occurring neuroglycopenic symptoms. This disorder is observed more often in women, usually those in a health-related occupation (Service, 1995). In our study, 48.10% patients (68% women) had factitious hypoglycemia induced by self-administration of insulin in suicidal attempt. None of our patients had a health-related occupation, but all of them had relatives treated with insulin for diabetes. Factitious hypoglycemia had to be distinguished from insulinoma (Table III.6), and insulin autoimmune hypoglycemia, because of their similar features (Service, 1995). Diagnosis of artificial or factitious hypoglycemia is based on dosage of OHA in the blood or urine. A quantitative method for determining serum levels of OHA, which proved to be as much useful as high-pressure liquid chromatography is capillary electrophoresis (Paroni et al., 2000). Other non-diabetic drugs have hypoglycemia as complication when administered in therapeutic doses, or in overdosage. The mechanism of salicylates-induced hypoglycemia is mediated by enhanced insulin secretion, but extra-pancreatic mechanisms cannot be excluded. Thus, aspirin stimulates muscle glucose uptake, and suppresses the release of fatty acids from adipose tissues in hypoglycemia (Fang et al., 1968; Baron, 1982). Propranolol, in addition to masking the epinephrine-related early symptoms of hypoglycemia, inhibits muscle glycogenolysis and peripheral glucose utilization and blunts the glucagon response to insulin-induced hypoglycemia (Ben-Ami et al., 1999; Lionte et al., 2002).

Morbidity of severe hypoglycemia is well recognized in diabetic patients. Sequelae of hypoglycemia occurred in 46% patients, as shown in a study on acute hypoglycemia requiring hospitalization, published in 1998 (Hart & Frier, 1998). Most reports on hypoglycemia-related morbidity emphasize the effects of neuroglycopenia on the central nervous system or

associated vascular events, such as myocardial infarction, stroke, and cardiac arrhythmias, and rarely musculoskeletal injuries (Ben-Ami et al., 1999; Chinnapongse et al., 1998; Bologa et al., 2002; Lionte et al., 2002; Chang et al., 2007; Laitinen et al., 2008; Gill et al., 2009).

Table III.6. Differential diagnostic between factitious hyperinsulinemia and insulinoma (adapted from Lebowitz & Blumenthal, 1993)

Test	Insulinoma	Exogenous insulin	Sulfonylurea
Plasma insulin	Increased (up to 1435 pmol/L)	Very much increased (> 7175 pmol/L)	Increased
Insulin/glycemia ratio	Increased	Very much increased	Increased
Proinsulin	Increased	Normal/decreased	Normal
C peptide	Increased	Normal/decreased*	Increased
Anti-insulin antibody	Absent	+/-	Absent
Plasma or urinary sulfonylurea	Absent	Absent	Present

* C peptide level can be normal in absolute values, but decreased compared to increased value of insulin; thus molar ratio insulin/ C peptide in venous blood > 1.0 in patients with hypoglycemia is suggestive for surreptitious administration or inadequate doses of insulin, excluding insulinoma or sulfonylurea overdose.

Our results evidenced that, in patients with DIHC, morbidity of hypoglycemia was present in 27.85% patients and was represented by recurrent episodes of hypoglycemia in 15.19% patients poisoned with anti-diabetic agents, arrhythmias (8.86%), transient focal neurological disturbances (2.53%) and acute pulmonary edema (1.26%). The common pathway to acute pulmonary edema in the presence of hypoglycemia is having one or more seizures, hypothesis that strongly supports the neurogenic mechanism in development of hypoglycemia-associated pulmonary edema. Thus, sympathetic hyperstimulation as a consequence of disturbances in subthalamic nucleus and hypothalamus induces lymphatic vasoconstriction and platelet aggregation, which causes micro emboli. The hydrostatic pressure increases in pulmonary capillaries and, in addition, disruption of alveolocapillary membrane damaged by long-lasting hypoglycemia (its integrity depends on glucose metabolism) could explain the development of acute pulmonary edema (Lionte et al., 2004). Mortality in our study was 2.53%, as a direct consequence of severe heart rhythm disturbances in those patients. In other studies, mortality from hypoglycemia ranged from 7 to 11%, and in one study involving hypoglycemic coma in diabetic subjects, death occurred in 4.9% patients (Hart, 1998; Ben-Ami et al., 1999).

The initial approach of a patient presented with altered mental status in ER should include the following ABCs: intravenous (IV) access, oxygen, monitoring, and rapid determination of blood glucose (Accu-Check®). Administration of glucose as part of the initial evaluation of altered mental status often corrects hypoglycemia. Treatment should not be withheld while waiting for a laboratory glucose value. Because the brain uses glucose as its primary energy source, neuronal damage may occur if treatment of hypoglycemia is delayed (Lionte, 2004). In patients with hypoglycemia without diabetes mellitus, the following strategy is recommended: first, pursuing clinical clues to potential hypoglycemic etiologies - drugs (insulin or insulin secretagogue treatment for diabetes mellitus is the most common cause of hypoglycemia), critical illnesses, hormone deficiencies, non-islet cell tumors. In the absence of these causes, the differential diagnosis narrows to accidental, surreptitious, or even malicious hypoglycemia or endogenous hyperinsulinism. In patients suspected of having endogenous hyperinsulinism, plasma glucose, insulin, C-peptide, Proinsulin, beta-hydroxybutyrate, and circulating oral hypoglycemic agents during an episode of hypoglycemia must be measured and insulin antibodies should be measured (Cryer et al, 2009). If hypoglycemia is confirmed,

the patient may be treated with an IV injection of glucagon and the plasma glucose response monitored (because this action has a high likelihood to provide both diagnostic data and effective treatment). Depending on the response, patients may require IV glucose, administered either as bolus of 33-50% solution or a continuous infusion of 10% intravenous glucose and plan to maintain it uninterruptedly for 1 or more days, with added glucagon, and diazoxide administration, if necessary, until sustained hyperglycemia guarantees that all drug effects are worn off (Service, 1995; Lionte et al., 2003; Seltzer, 1989). The over-treatment of hypoglycemia in a nondiabetic person has no bad effects (Service, 1995). The approach to treatment of the underlying cause of hypoglycemia depends on the specific causal mechanism. In acute intoxications complicated with hypoglycemic coma, measures directed to toxin removal, such as activated charcoal, laxatives, and gastric lavage are appropriate. Continuous veno-venous hemofiltration improves toxin removal, corrects metabolic and electrolytic disorders in situation of multiple ingestions, and must be used in patients admitted in ICU (Lionte et al., 2006).

Patients in our study received as first line therapy IV Glucose, administered either as bolus of 33-50% solution or as a continuous infusion of 10% intravenous Glucose in all cases. Also, we applied measures of gastric decontamination and toxin removal, including special means, such as continuous veno-venous hemofiltration. We administered glucagon in 19% patients with beta-blocker and OHA overdose. Glucagon is indicated in beta-blocker poisoning because it stimulates production of cAMP through non-adrenergic pathways, resulting in enhanced myocardial contractility, heart rate, and AV conduction. It is effective in treating beta-blocker-induced hypoglycemia only if sufficient liver glycogen is present, because hepatic glycogen availability is necessary to treat hypoglycemic patients; glucagon has virtually no effects in patients with starvation, adrenal insufficiency, or chronic hypoglycemia (Bologa et al., 2002; DeWitt & Waksman, 2004). Octreotide was used only in 7.59% patients with sulfonylurea overdose, mainly because it was not available in hospital before 1998. Octreotide is a somatostatin analog which acts primarily on somatostatin receptor subtypes II and V, inhibits GH secretion and has a multitude of other endocrine and non-endocrine effects, including inhibition of glucagon, VIP, and GI peptides, and inhibits insulin release. Glucose itself induces insulin secretion thus theoretically contributing to rebound hypoglycemia when used to treat hypoglycemia. Octreotide is thought to block the elevated insulin levels that are a result of both the sulfonylureas and dextrose. Recent case reports and one prospective study in healthy volunteers have demonstrated the safety and efficacy of octreotide administration for the treatment of sulfonylurea induced hypoglycemia. Based largely on the results of these studies some experts in the field of toxicology have argued that administration of octreotide be standard therapy for all patients with recurrent hypoglycemic episodes induced by sulfonylureas. Octreotide is safe and effective in preventing rebound hypoglycemia after sulfonylurea ingestion and, in combination with glucose, it should be considered for first-line therapy in the treatment of sulfonylurea-induced hypoglycemia (McLaughlin et al., 2000; Fasano et al., 2008; Stanescu et al., 2006).

Conclusion

Most cases of acute exogenous poisoning are intentional and occur in young women. There is an increasing number of acute poisonings in patients from urban regions. In non-diabetic subjects, hypoglycemia is induced mainly by ethanol poisoning, beta-blocker overdose, toxic mushroom poisoning, salicylate overdose. Self-administration or ingestion of anti-diabetic agents (insulin or sulfonylureas and biguanides) cause factitious hypoglycemia, but fortunately this condition is rare in clinical practice (43 patients in 10 years). We demonstrate that a useful test to assess toxic-induced hypoglycemia is standard 6-hour OGTT,

because only determining blood glucose level is not always enough. Factors predicting a negative outcome in toxic-induced hypoglycemia are association of toxins (biguanides and ethanol), cardiac, hepatic and renal complications and age (> 65 years). In non-diabetic subjects with acute poisoning, prevalence of toxic-induced hypoglycemia depends on the poison itself, the mechanism of poisoning, also depends on the association between toxics and on the severity of toxic- induced liver disease.

As for DIHC, it is a serious event, yet rarely encountered in clinical practice (0.78% admissions for drug overdose). In acute poisonings, anti-diabetic drugs (insulin and OHA) in 91.14% cases, followed by beta-blockers (6.33%), and salicylates (2.53%) produced DIHC. Anti-diabetic drugs, followed by the association of drugs with hypoglycemic risk, and association of alcohol intake to a drug overdose with hypoglycemic potential, produced the most severe forms of hypoglycemia. Cardiovascular morbidity was the main complication of DIHC. Arrhythmias represented the cause of death in subjects with DIHC, even in the absence of a previous cardiovascular disease. Treatment of DIHC in a non-diabetic subject includes, along with measures directed to drug removal, IV glucose, glucagon and octreotide.

III.1.4. Rare complications after drugs and environmental agents' exposure

This direction of research is reflected in the following published articles:

1. Sorodoc, L; **Lionte, C; (correspondent author),** Bologa, C; Petris, O; Sorodoc, V; Buga C. Acute pancreatitis after nifedipine and acetaminophen poisoning - case report. *Cent Eur J Med* 2009; 4(4): 527-531. DOI: 10.2478/s11536-009-0057-y (ISSN 1895 –1058) (**FI 0.224**)
2. Bologa, C; **Lionte, C (correspondent author);** Ursaru, M; Sorodoc, L; Coman, EA; Puha, G; Petris, OR. An unusual etiology of acute necrotic pancreatitis in a comatose patient. *J Emerg Med Case Reports* 2019; 10(2): 43-46. (ISSN 2149-9934) **Emerging Sources Citation Index (ESCI)**
3. Petris, OR; Bologa, C; Sorodoc, V; **Lionte, C.** Repeated Bronchoscopy - Treatment of Severe Respiratory Failure in a Fire Victim. *J Crit Care Med* 2017; 3(4): 162-165. DOI 10.1515/jccm-2017-0024 (ISSN 2393-1809) **Emerging Sources Citation Index (ESCI)**
4. **Lionte C**, Sorodoc L, Sorodoc V, Petriş O. Self-administration of intravenous drugs-a rare cause of respiratory arrest in medical practice. *Rev Med Chir Soc Med Nat Iasi.* 2007; 111(1):111-4. (ISSN: 0048-7848) **PMID: 17595854**
5. **Lionte C**, Şorodoc L, Laba V. Respiratory syndromes in acute poisoning. *Rev Med Chir Soc Med Nat Iasi* 2004; 108(3): 547-551. (ISSN: 0048-7848). **PMID: 15832971**

Drug-induced acute pancreatitis

Background

Certain drugs have well documented associations with acute pancreatitis (AP). Case reports of drug-induced AP that involved at least 40 of the top 200 most prescribed medications in 2007 have been published (Kaurich, 2008). Although calcium-channel blockers have been cited as the cause of drug-induced pancreatitis (DIP), nifedipine was not among them. Acetaminophen, on the other hand, has been cited in association with DIP (Table III.7), occurring in up to 36% of cases of severe paracetamol poisoning (Badalov et al., 2007; Eltookhy & Pearson, 2006). Acute pancreatitis secondary to a drug overdose is rare in clinical practice, representing at most 2% of the total cases (Hammad & Fawzi, 2000; Urbanek et al., 2012). The first case of drug-induced acute pancreatitis after chlorthalidone and cortisone

was reported in 1955. The list of drugs responsible for this complication has increased to about 500 agents (Cofini et al., 2015). Only statins, diuretics, antiretroviral agents, and anticonvulsants are responsible for acute necrotic pancreatitis (Ali & Loh, 2013; Jones et al., 2015). The incidence of acute pancreatitis induced by chronic valproate therapy increased since 1979, when the first case was reported, because of its extensive use in the medical practice (Hurdle & Moss, 2009; Sikma, 2008; Atam et al., 2017). The usual toxic effects after an acute valproate overdose are: central nervous system depression, gastro-enteral effects, pancreatitis, metabolic acidosis with a high anionic gap, dyselectrolytemia and hyperammonemia (Hammad & Fawzi, 2000; Sikma, 2008; Wilimowska et al., 2006). All published literature on the subject reveals this complication only after chronic therapy with valproate for different conditions, or after valproic acid overdose in patients already using this drug. Currently, there are no reports of patients with necrotic pancreatitis as a complication of valproic acid acute overdose, in patients naïve to valproate therapy.

Table III.7. Examples of drugs associated with pancreatitis
(adapted from Badalov et al., 2007; Eltookhy & Pearson, 2006; Trivedi& Pitchumoni, 2005)

	Class Ia	Class Ib	Class II	Class III	Class IV
Antibacterials, antifungals, antivirals	Isoniazid Metronidazole Tetracycline.	Pentamidine Trimethoprim-sulfamethazole Lamivudine	Erythromycin Rifampicin	Ceftriaxone Clarithromycin Ribavirin	Azithromycin, amoxicillin, ciprofloxacin, fluconazole, penicillin, ganciclovir.
Anti-inflammatory, analgesic agents	Codeine Sulindac	-	Acetaminophen	Indomethacin Prednisone	Celecoxib, colchicine, diclofenac, meloxicam, naproxen, piroxicam.
Cardiovascular agents	Enalapril Procainamide	Furosemide Amiodarone	Hydrochlorothiazide	Captopril Irbesartan	Amlodipine, atenolol, lisinopril, candesartan, mexilitine, ramipril.
Gastrointestinal medication	Mesalamine, sulphasalazine	Omeprazole	-	-	Cimetidine, famotidine, ranitidine ondansetron, pantoprazole.
Miscellaneous	Cannabis Carbimazole	Methimazole	Propofol	Alendronate	Calcitriol, contrast media, glimepiride, glyburide, pilocarpine, repaglinide.

Class Ia: at least 1 case report with positive rechallenge, excluding all other causes, or more than 20 cases of acute pancreatitis reported; Class Ib: at least 1 case report with positive rechallenge, other causes, and other drugs were not ruled out; Class II: at least 4 cases in the literature, consistent latency (≥75% of cases); Class III: at least 2 cases in the literature, no consistent latency among cases, no rechallenge; Class IV: single case report published in medical literature, without rechallenge.

Patients and methods

Our aim was to present diagnostic challenges faced by Emergency Department (ED) physicians in the management of a comatose patient with a rare form of acute pancreatitis. A case of severe nifedipine and acetaminophen poisoning with prolonged collapse was complicated by acute pancreatitis and multiorgan failure, which responded to intensive treatment, including continuous veno-venous hemofiltration (CVVH). We report here the first case of acute necrotic pancreatitis in a 22-year-old comatose woman with valproic acid acute overdose in attempted suicide, a patient naïve to valproate therapy.

Results

We first reported a case of a 23-year-old woman who was admitted 9 hours after ingesting approximately 300 tablets of 10-mg slow-release nifedipine (3 g, 60 mg/kg) and an unknown amount of acetaminophen in a suicide attempt. Her past medical history was unremarkable. At the time of presentation, she was awake, with tinnitus, nausea, palpitations, and chest tightness. Physical examination revealed pallor of the skin, cyanosis of the extremities, tachypnea (32 respirations per minute), and tachycardia (120 beats per minute),

severe hypotension (blood pressure 60/40 mm Hg), and decreased bowel sounds. The electrocardiogram showed sinus tachycardia with normal intervals and a slight ST-T abnormality. Initial laboratory data and that obtained subsequently during hospitalization are presented in Table III.8. Nifedipine plasma levels measured by gas chromatography 36 hours post-ingestion were 509 μg per liter, and the estimated peak level was up to 2,000 μg per liter (therapeutic range, 25 to 100). Acetaminophen levels 9 hours after ingestion were 184 μg per milliliter. The other results of toxicologic screening (including blood alcohol level) were negative. Ultrasound examination of the abdomen showed a nonhomogeneous, edematous pancreas, with no evidence of gallstones or biliary tree dilatation, obstruction, or both. An abdominal CT scan revealed an inflamed pancreas, but no evidence of necrosis. Endoscopic study was also normal. Serologic tests for hepatitis B, echovirus, parotiditis, and coxsackievirus showed no evidence of recent infection. Hypotension persisted despite treatment with gastric lavage, activated charcoal, aggressive hydration, intravenous calcium chloride, glucagon, and combination vasopressor therapy.

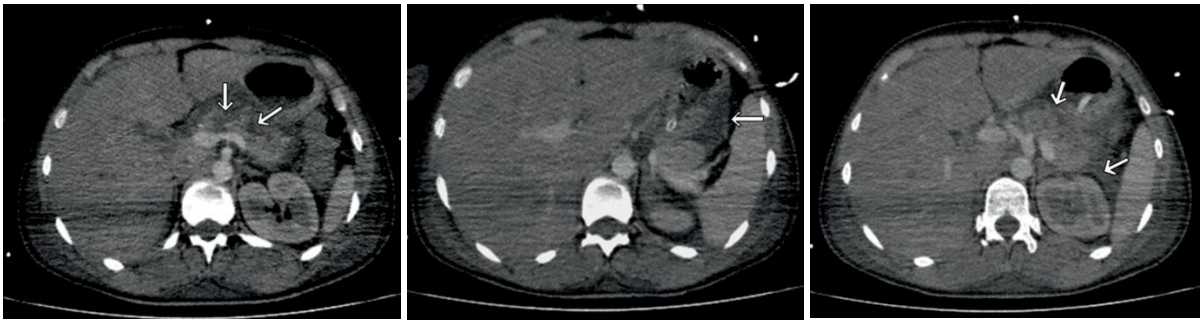
Table III.8. Laboratory values during the hospital admission

	Units	Reference range	Admission	1st day	2nd day	3rd day	4th day	7th day	9th day
WBC (white blood cell count)	x 10^3 /l	4-8	15.4	18.8	21.3	10.9	8.4	8.1	7.4
Hematocrit	%	36-46	31.6	27.1	26.7	22.1	21.1	31	37
ESR (erythrocyte sedimentation rate)	mm/h	0-10	34	54	92	-	-	30	25
Amylase blood	IU/L	20-110	570	482	471	144	97	66	45
Amylase urine	IU/L	32-641	130	380	1770	731	527	-	348
Lipase	IU/L	22.9-300	1699	825	232	117	187	253	158
Blood glucose	mg/dl	65-100	498	96	112	96	136	81	106
AST (Aspartate aminotransferase)	IU/L	15-50	37	28	131	601	111	37	34
ALT (Alanine aminotransferase)	IU/L	10-70	24	24	71	427	213	78	56
γGT (Gamma-glutamyltranspeptidase)	IU/L	8-78	-	17	-	15	-	60	48
ALP (Alkaline phosphatase)	IU/L	38-126	-	43	-	52	-	48	42
Bilirubin	mg/dl	0.2-1.3	1	1	1	1.1	0.7	0.8	0.8
Calcium (Ca++)	mmol/l	1.13-1.32	0.92	1.17	1.16	1.14	1.1	1.06	1.19

Antidotal therapy for acetaminophen overdose (Doyon & Klein-Schwartz, 2009) consisted of N-acetylcysteine, with an initial loading dose of 150 mg per kilogram over a period of 15 minutes, followed by 50 mg per kilogram over a period of 4 hours, and then 100 mg per kilogram over the period of the next 16 hours (total dose, 300 mg/kg). Twenty-four hours after presentation, she was intubated for respiratory distress and altered mental status (Glasgow Coma Scale 8) and remained hypotensive and oliguric. She required vasopressors for the next 48 hours and respiratory support for the next 4 days. Supplemental oxygen was administered during the first 5 days, bedside oxygen saturation was monitored at frequent intervals, and blood gases were obtained when clinically indicated. CVVH was initiated within 48 hours after admission because of renal failure and metabolic acidosis (pH 7.16). Sepsis, hepatic cytolysis, and bilateral pleurisy delayed further recovery. Ten days following the drug ingestion, mentation and blood tests were normal, and she was discharged to an outside facility for rehabilitation.

Another report describes the case of a 22-year-old female patient, without significant medical history, who was brought unconscious to the ED. The empty boxes for approximately 60 pills of 300 mg valproate sodium extended release were found at her residence. The family reports no chronic medical therapy, no alcohol, tobacco or drug use in this patient.The last contact with the patient was more than 24 hours before presentation. Upon admission to ED, the patient had a Glasgow Coma Scale score of 3, respiratory

depression, a blood pressure of 100/60 mmHg, and a regular heart rate of 108 beats/min. She was intubated and mechanically ventilated. A cranio-cerebral CT scan was performed and revealed no abnormalities. Blood tests showed increased glucose (127 mg/dl), ammonia (98 mmol/L), calcium (6.63 mg/dl), lactate (37 mg/dl), CK (1471 U/L), amylase (2989 U/L) and lipase (1328 U/ L). Toxicological screen for drugs and alcohol was negative. The serum valproate level was 105 mg/L in our patient. The therapeutic reference range for valproate is 50-100 mg/L (Wilimowska et al., 2006). The increased values of amylase and lipase, in the absence of a medical history of gallbladder disease or ultrasound changes of the gallbladder, lead to a suspicion of pancreatitis, confirmed by a contrast-enhanced abdominal CT scan (Figure III.8), revealing specific changes of acute necrotic pancreatitis, with a Balthazar score of 5. We excluded another etiology for necrotic pancreatitis. We initiated only supportive treatment, parenteral hydration with crystalloid solutions 250 ml/h for the first 48 hours, and correction of electrolytes. Seventy-two hours from admission in our department, the patient regained consciousness and declared the ingestion of Depakine Chrono ®, her father's medication for a psychiatric condition. She had no abdominal complaints during hospitalization. The evolution was favorable, with pancreatic enzymes normalization 14 days from the moment of admission. An abdominal CT scan 15 days later showed the presence of pancreatic pseudocysts, treated conservatively.



A. Non-homogeneous pancreatic structure, with necrotic areas (arrows).

B. Liquid collection with a thin iodophile wall, near the large curb of the stomach (arrow).

C. Infiltrates of the peri pancreatic fat, and a liquid fuse expanded into anterior left pararenal area (arrows).

Figure III.8. Contrast-enhanced CT scan shows evidence of necrotic pancreatitis.

Discussion and conclusions

DIP is considered to be rare (2%), and to make the diagnosis, other possible causative factors must be ruled out (Mallick, 2004). This case shows an association between nifedipine and acetaminophen overdose and AP in a previously healthy young woman. The common causes of pancreatitis, such as gallstones, alcohol abuse, hypercalcemia, hypertriglyceridemia, viral infection and trauma were excluded in this patient. A number of drugs, such as cardiovascular agents and anti-inflammatory analgesic agents can cause pancreatitis in adults (Mallick, 2004). Among calcium-channel blockers, only amlodipine has been associated with DIP (Eltookhy & Pearson, 2006). The most important clinical effect of calcium-channel blockers is on cardiac myocytes, cardiac conductive tissue, vascular smooth muscle, and pancreatic beta cells; overdoses may result in hypotension, bradycardia, altered mental status, sinus arrest, various cardiac conduction delays, nausea, vomiting, and metabolic acidosis with hyperglycemia (Harris, 2006). Many of these features were seen in this patient. This patient, who had a massive overdose of nifedipine, which acts mostly on peripheral arterial smooth muscle, presented with marked hypotension and an elevated heart rate.

Cytochrome P-450 3A4 (CYP3A4) is responsible for the metabolism of numerous therapeutic agents, including nifedipine and acetaminophen. Experimental studies on drugs also metabolized by CYP3A4 have shown that acetaminophen inhibits metabolism of these drugs in a noncompetitive fashion (Feierman, 2000). On the other hand, studies on rat hepatocytes have demonstrated that under in vitro conditions, nifedipine pretreatment exhibits a preventive effect against acetaminophen induced hepatocyte injury (Dimova et al., 1995). We may suppose that nifedipine protected our patient against acetaminophen induced liver injury, although there are no clinical studies to demonstrate this effect in humans.

Pancreatic injury may result from splachnic hypoperfusion after circulatory shock (Manjuck et al., 2005). Ischemic injury to the pancreas occurs in specific clinical settings, such as cardiopulmonary by-pass, surgery for thoraco-abdominal aneurysms, haemorrhagic shock, and transplantation of the pancreatic gland (Sakorafas et al., 2000). Experimental studies have shown that ischemia may induce AP. Ischemia followed by reperfusion results in a breakdown of the microcirculation in the pancreas as in other organs, and it is considered to be a critical factor in the pathogenesis of AP (Pezzilli et al., 2002). Ischemic injury to the pancreas is one factor that contributes to increases in serum lipase and amylase in critically ill patients (Manjuck et al., 2005).

In our case, we believe that ischemia secondary to profound hypotension induced by massive nifedipine overdose contributed to the development of AP and elevation of serum pancreatic enzymes. Paracetamol poisoning has mainly been associated with hepatotoxicity. Pancreatitis, cardiotoxicity, and hematotoxicity are among the more unusual complications of paracetamol poisoning. Hyperamylasemia may simply reflect direct paracetamol-induced pancreato-toxicity resulting in predominantly subclinical pancreatic damage. A clinical diagnosis of AP is made in 14% of cases with paracetamol-associated hyperamylasemia (Schmidt & Dalhoff, 2004). The acetaminophen level was consistent, in our case, with a mild form of poisoning and could have contributed to pancreatic injury produced by ischemia. We believe that the liver enzymes were increased in the setting of ischemic liver injury, not as a hepatotoxic effect of acetaminophen. Liver toxicity is defined as serum aspartate aminotransferase or alanine aminotransferase levels greater than 1000 IU per liter in acetaminophen poisoning (Doyon & Klein-Schwartz, 2009). In this case early initiation of antidotal therapy (9 hours after ingestion) could have contributed to low levels of aminotransferases.

For a diagnosis of AP, two of the following three features are required: 1) abdominal pain characteristic of acute pancreatitis; 2) serum amylase and/or lipase levels $\geq$ 3 times the upper limit of normal; 3) characteristic findings of AP on CT scans (Banks et al, 2006). This case fulfilled all of these criteria. Based on the tests performed on admission (APACHE-II score < 8 and serum hematocrit <44), our patient had mild AP. Among the single-organ failures in AP, pulmonary failure is the most common in cases of severe AP (Zhu et al., 2003). Our patient had respiratory distress 24 hours after presentation, and she required intubation and mechanical ventilation for the next 4 days.

Early vigorous intravenous-fluid replacement is of foremost importance in AP for decreasing the hematocrit and restoring normal cardiocirculatory functions (Beger & Rau, 2007). Our patient was admitted to an intensive care unit because of organ failure, oliguria, persistent tachycardia, and labored respiration. Treatment in this case consisted of supportive care including vigorous fluid resuscitation monitored by a progressive decrease in serum hematocrit at 12 and 24 hours. The patient in this case resumed oral nutrition within 5 days and did not require nutritional support. Early preemptive application of CVVH in the treatment of severe AP can modulate systemic inflammatory response syndrome and consequently diminish the incidence of systemic complications (Pupelis et al., 2007). We used CVVH in our case

within 48 hours of admission, on the basis of the experience reported in renal failure, in severe acidosis, and in several cases of acute poisoning, including one with nifedipine (Lionte et al., 2006).

Valproic acid is one of the new antiepileptic drugs used extensively in the last twenty years for epilepsy, bipolar affective disorders, schizophrenia, and for migraine attacks prophylaxis (Wilimowska et al, 2006). Literature has recorded numerous information on drug-induced pancreatitis (Table 1), and case reports of acute pancreatitis in patients with chronic valproic acid treatment, including acute necrotizing pancreatitis (Ali & Loh, 2013). All these case reports documented acute pancreatitis in patients already receiving valproate therapy since childhood, or after increasing the dose of a chronic valproate therapy (Ali & Loh, 2013; Pellock et al., 2002). However, there are no reports regarding necrotic pancreatitis after an acute overdose of valproic acid, in patients naïve to this treatment, or at first exposure to this drug. Acute pancreatitis induced by valproic acid is not dose dependent and is the result of an idiosyncratic reaction (Sikma, 2008; Wilimowska et al., 2006). The mechanism of acute pancreatitis induced by valproic acid overdose is not yet elucidated. The direct toxic effect of oxygen free species on pancreatic tissue, and the depletion of superoxide dismutase, catalase and glutathione peroxidase can be involved (Jones et al., 2015). There is no correlation between the serum level of valproic acid and the severity of the acute poisoning. The plasmatic peak of valproic acid occurs 18 hours from ingestion, and the half-life is up to a maximum of 48 hours, in the setting of an acute overdose (Sikma, 2008). Our patient, although presenting necrotic pancreatitis in the setting of an acute severe valproate poisoning, had a serum level of valproate corresponding to a therapeutic level. However, the assay was performed 48 hours from ingestion. The evolution was favorable, and the coma was resolved after 72 hours with supportive treatment. Although the profound coma was prolonged, cerebral CT scan showed no brain edema, which occurs 12 hours after valproic acid overdose and lasts for four days (Crudup et al., 2011). Pancreatitis' evolution was favorable with medical treatment. The patient was discharged 16 days later without complaints, with normal laboratory tests. Necrotic pancreatitis induced by a valproate overdose can be asymptomatic. The diagnosis in our patient was based on elevated pancreatic enzymes and imagistic tests, as literature suggests (Tenner et al., 2013).

In summary, we initially documented a clinical case of acute mild pancreatitis. The patient had no previous medical history of and no risk factors for the development of AP. Immediately preceding the onset of this episode, she had taken a dose of nifedipine, 60 mg per kilogram, combined with an unknown amount of acetaminophen, which resulted in profound hypotension. We excluded other causes of AP by clinical history, serum toxicology, serology, and abdominal imaging. In the absence of rechallenge, we believe that toxic doses of nifedipine are principally responsible for inducing AP by severe hypotension. We report this case because it has been found in some studies that high doses of nifedipine have had a beneficial effect on AP resulting from several causes (Słomka et al., 2001; Prat et al., 2002). To our knowledge, this is the first such case in the literature, and it reinforces the fact that drug-induced or aggravated AP is a problem of serious concern. We also reported the first case with necrotic pancreatitis induced by an acute overdose of valproic acid in a patient naïve to this treatment. A PubMed search using keywords:" valproate, poisoning, pancreatitis" showed only 21 papers, all revealing this complication after chronic therapy with valproate for different conditions, or after valproic acid overdose in patients already using this drug. The ED practitioners must be aware of this etiology of necrotic pancreatitis, especially in the assistance of unconscious patients having elevated levels of pancreatic enzymes, even if the patients are naïve to valproate therapy.

Respiratory syndromes in acute poisoning

Background

Respiratory syndromes (RS) in acute poisoning can refer to a wide range of specific clinical syndromes, from acute tracheobronchitis to acute pulmonary edema (APE), chemical pneumonia, acute respiratory distress syndrome (ARDS) and acute respiratory failure (ARF), that occur as a result of direct or indirect effect of chemical substances, drugs and toxins on lungs and airways. The association of toxins, inhalation of gases or volatile substances have a high risk for appearance of respiratory syndromes. Respiratory arrest is a major emergency in medical practice, which imposes a prompt intervention from the physician assisting such case. Respiratory arrest can be classified into primary respiratory arrest, caused by airway obstruction, decreased respiratory drive, or respiratory muscle weakness and secondary respiratory arrest, as a result of circulatory insufficiency. Among important causes of respiratory arrest, acute poisonings are to remember, especially opiate poisoning.

Aim of the research

Our study attempted to identify, during one-year retrospective study on patients diagnosed with acute poisoning, addressed to the Medical Clinic of Emergency Clinic Hospital of Iasi, the respiratory syndromes commonly associated with acute poisoning. We also reported a case of respiratory arrest following intravenous self-administration of opiates in attempted suicide.

Materials and methods

We performed a retrospective study on patients admitted to the Medical Clinic of the Emergency Clinic Hospital Iasi over a 12-month period, with a diagnosis of acute poisoning. We detected the main respiratory syndromes associated with acute poisoning, we made correlations with the route of exposure, combinations of poisons, associated comorbidities, we analyzed the evolution and the outcome of these syndromes. For each group, we calculated the mean and standard deviation. The comparison among groups was made using Student-Fischer t test.

Results

We reviewed the files of 262 patients hospitalized within a 12-month interval with a diagnosis of acute poisoning in our department. Forty patients out of 262 (15.27%) had respiratory syndromes. The baseline characteristics of these patients are presented in table III.9.

Table III.9. Baseline characteristics of acutely poisoned patients according to RS recorded

	Total (n = 262)	**RS (n = 40)**
Gender, M/F	91/171	14/26
Age, years	34.36 ± 15.52	39.05 ± 16.34
Poisoning's type (self-harm/accidental)	199/63	27/13
Poison type		
Drugs	147 (56.1%)	12 (30%)
Caustic substances	44 (16.79%)	11 (27.5%)
Pesticides	23 (8.77%)	7 (17.5%)
Carbon monoxide (CO)	8 (3.05%)	8 (20%)
Organic solvents	3 (1.14%)	2 (5%)
RS		
Acute tracheobronchitis & laryngitis	-	14 (35%)
Chemical pneumonitis	-	1 (2.5%)
APE	-	10 (25%)
ARDS	-	1 (2.5%)
ARF	-	14 (35%)

The substances responsible for acute poisoning associated with RS were: pharmaceutical agents – 12 patients (30%), caustic agents – 11 cases (27.5%), CO – 8 patients (20%), organophosphate and organochlorine pesticides – 7 cases (17.5%) and solvents. For 19 patients (47.5%) the acute self-harm poisoning was the first suicide attempt. The association of poisons with a synergic effect was noticed to be with ethanol – 12 cases (30%), and combination pesticides + drugs (1 case) or pesticides + caustics (1 case). The route of exposure was respiratory in 11 patients (27.5%) and oral for the rest of 29 cases (72.5%). We found a statistically significant correlation between the respiratory route of exposure and the occurrence of RS in acute poisoning ($p < 0.05$).

A special situation was of a male patient, brought in the ED by his family. Upon admission he was unconscious, presenting cyanosis of the extremities, without spontaneous respiration. The family declared that the patient, after a conflict with a family member, injected himself IV a vial of Morphine (1 ml, morphine chlorhydrate 20 mg/mL) from his mother's medication (oncology patient). Physical examination reveals a severe condition, cyanosis of the extremities, puncture site at the left arm, profuse sweats, no respiratory movements, normal cardiac sounds 76/min, blood pressure (BP) 130/80 mmHg, miosis, coma with a GCS score of 4. Paraclinical tests showed leukocytosis 9,300/mmc, alkali reserve (AR) 20 mEq/L, pH 7.3, SaO2 41%. The blood glucose, BUN, creatinine, electrolytes, transaminases were all normal. ECG reveals normal sinus rhythm 68/minute, QRS axis + 45°, normal morphology. Toxicological screens revealed the presence of opiates, with absence of barbiturates, benzodiazepines, and organophosphate pesticides. The patient was immediately intubated and mechanically ventilated, with oxygen administration. Antidote was administered – nalorphine initially 10 mg IV, followed by 1 mg in 15 minutes, up to a total amount of 14 mg, together with supportive therapy (crystalloid solutions, group B vitamins, piracetam, aminophylline). The outcome was favorable, and the patient recovered consciousness, was extubated 4 hours later, and discharged completely recovered after 24 hours.

A major problem encountered in the diagnosis and therapy of those patients is represented by the presence of comorbidities. The recorded comorbidities were, in order of the frequency: ethanol addiction – 5 cases, bronchial asthma – 5 patients, chronic hepatitis – 4 cases, hypertension – one case, rheumatic valve disease complicated with left ventricular failure – one patient, pneumonia before the occurrence of poisoning – 1 case. The rest of the patients were apparently healthy before the acute poisoning. No deaths were noticed in the population analyzed; all 40 patients who developed RS had a favorable outcome after the intensive care provided.

Discussion and conclusions

Toxic tracheobronchitis is characterized by acute exudative and necrotic inflammation, of various degrees, of the airway mucosa, as a result of chemical aggression after irritant gases, volatile toxic substances or caustic agents' inhalation (Mogos & Sitcai, 1988). In severe forms, nasal mucosa is also affected. When bronchospasm is associated, an obstructive syndrome and asphyxia occurs. Also, extensive laryngeal edema which can occur in this situation leads to acute glottic edema and respiratory distress, making the orotracheal intubation impossible, as it happens in acute caustic substances poisoning (Bologa et al., 2000). In our study, acute tracheobronchitis was recorded in poisoning with caustic substances, CO and organic solvents.

APE is a major syndrome within toxin-induced RS. Based on pathophysiology, APE can be classified into four categories: 1) secondary to increasing the hydrostatic pressure (hemodynamic), as it is the situation in meprobamate or barbiturate acute poisoning; 2) after alveolar diffuse injury followed by increasing the permeability of alveolo-capillary membrane (the most severe clinical form is ARDS); 3) secondary to increased permeability of the alveolo-capillary membrane, without diffuse alveolar injury (such as APE induced by cocaine, "crack"

and heroin overdose); 4) following a mixt mechanism with increased hydrostatic pressure and permeability changes (Mogos & Sitcai, 1988; Gluecker et al., 1999). Non-cardiogenic APE and ARDS are frequent clinical conditions within drug-induced pulmonary injury. Clinical and radiological picture is similar with APE and ARDS induced by other etiologic factors. Clinical manifestations consist of dyspnea, chest discomfort, tachypnea, hypoxemia and respiratory alkalosis (Lee-Chiong & Matthay, 2004; Mortelliti & Manning, 2002). Cardiomegaly and redistribution of pulmonary circulation, which are characteristic for cardiogenic APE, are generally missing, except for the patients who have a previous cardiac condition. This was the case of a patient in our study, who was admitted for an accidental poisoning after exposure to detartrant and chlorine vapors, who had a medical history of mitral and aortic regurgitation complicated with left ventricular failure. Another particular issue is when the toxin induces toxic myocarditis and cardiomegaly, in this situation the APE has a mixed cause (cardiogenic and acute lung injury). This is the case of acute poisoning with organophosphates, organic solvents, CO and cocaine. A special mention must be made for APE in organophosphates poisoning, when alveolar ducts are flooded with bronchial secretions after toxin- induced parasympathetic overstimulation and injury of the mucinous cells from the bronchial epithelia. As pathophysiological mechanisms in this situation, injury of alveolo-capillary membrane, altered myocardial contractility are also involved (Voicu, 1997). In our study, APE was recorded after pesticide, barbiturate, CO and organic solvents acute poisoning.

Acute chemical pneumonia (ACP) is the consequence of exposure to toxic gases, responsible for pulmonary injury, affecting alveolar surfactant, vessels, terminal bronchiole and interstitial space. Also, poisoning with ingested chemical substances which have a pulmonary elimination or have a direct effect on lungs may lead to ACP (Mogos & Sitcai, 1988). Among these toxins, ammonia, gasoline, kerosene, organophosphates, diesel and petroleum are to be mentioned. In our study, we recorded a single patient with ACP after accidental ingestion of kerosene.

ARDS, described for the first time in 1967 by Ashbaugh et al., is redefined in 1994 by a committee of European and American experts, as a syndrome with acute onset, characterized by bilateral infiltrates of chest X-ray, pulmonary capillary wedge pressure < 18 mmHg, or absence of clinical signs of increased pressure in the left atrium and PaO2/FiO2 < 200, where PaO2 is partial pressure of arterial oxygen and FiO2 is the fraction of inspired oxygen (Ware & Matthay, 2000). Etiopathogenesis of ARDS is represented by direct pulmonary injury, as is the situation of inhaling toxic gases and fumes, or aspiration of the gastric content. Also, indirect aggression mechanisms are involved, as is the case of drugs overdose, or poisoning with colchicine, toxic oils, ethchlorvynol, bromine carbide (Mogos & Sitcai, 1988; Esteban et al., 1983; Jebson et al., 1989).

Acute respiratory failure (ARF) is one of the major complications in acute poisoning, and one of the RS which mandates a rapid diagnosis and intensive care. The mechanisms involved in toxin-induced ARF are presented in table III.10.

In our study, 14 out of 36 patients with RS developed ARF, in poisoning with CO, CNS depressants (barbiturates, benzodiazepines, antidepressants, sedative-hypnotics), pesticides, caustic vapors and organic solvents. We've noticed that exposure after inhalation is always associated with RS, but also ingestion of organophosphates, organic solvents and caustics can lead to APE or ARF. Combination of poisons, such as pesticide + caustic increases the severity of lung injury, leading to major clinical syndromes. The outcome of RS depends on the time of exposure (for inhaled substances), and the early first aid and intensive care. For ingested substances followed by lung injury, the early admission and decontamination measures, with all the necessary precautions in case of an altered mental status, after stabilizing life-threatening conditions, such as APE and ARF, are of most importance.

Table III.10. Causes of ARF in acute poisoning (adapted from Mokhlesi et al., 2003)

Mechanism	Substance
Decreased ventilation	Alcohols, central nervous system depressants, strychnine, etc.
Aspiration	Toxins leading to an altered mental status.
Pneumonia	Toxins leading to bronchial aspiration or irritant gases.
Cardiogenic APE	Antiarrhythmics, betablockers, tricyclic antidepressants.
Acute lung injury leading to APE	Cocaine, ethylene glycol, salicylates, hydrocarbons, etc.
Inhalation of inert gases	Carbon dioxide, methane, nitrogen, propane.
Bronchospasm	Cocaine, heroin, organophosphates, myocardial toxins.
Alveolar hemorrhage	Anticoagulants, cocaine, amiodarone, thrombolytics, toluene, nitrofurantoin, penicillamine.
Pneumothorax	Cocaine, gas emboly after IV drugs administration.
Cell hypoxia	CO, cyanides, sulphate hydrogen, toxins leading to acquired methemoglobinemia (benzocaine, phenazopyridine, dapsone, and nitrates/nitrites).

Respiratory arrest is a complication of RS in several acute poisoning cases, such as CNS depressants, CO, organophosphates, cyanide, opiates, myorelaxant and toxins leading to acquired methemoglobinemia (Bologa et al., 2001; Varga & Somogyi, 1988). Opiates are opioid receptor agonists. The stimulation of these receptors in CNS leads to analgesia, vomiting and profound sedation, in a dose-dependent manner. The effects are potentiated by other sedatives (i.e., benzodiazepines) or alcohol (Lionte & Frasin, 2005; Buajordet et al, 2004). After absorption, opiates are metabolized in the liver. Morphine, an opioid analgesic, starts its action in 15 minutes after IV administration, and has a half-life time of 2-4 hours (Hoffman & Goldfrank, 1995). Morphine leads to respiratory depression after a direct action on respiratory centers in the brainstem. The respiratory depression is secondary to a decreased response of these centers to increased PaCO2 and electrical stimuli (Lionte & Frasin, 2005). The respiratory complications of acute opiate poisoning are acute lung injury leading to APE and broncho-aspiration (Buajordet et al, 2004). The management of the poisoning involves, in the presence of respiratory distress, airway management and repiratory support with orotracheal intubation and mechanical ventilation (Lionte & Frasin, 2005; Buajordet et al, 2004). The antidote treatment with naloxone, a pure opioid antagonist, reverses the sedative effect and respiratory depression of opiates and opioids. It can be effective also for mixed poisoning, with an opiate and another sedative agent. Naloxone is an antagonist of opioid receptors, with a short half-life time, which is administered IV in doses of 0,4-2 mg (Hoffman & Goldfrank, 1995). The effect lasts 1-2 hours after a single dose. Since the morphine half-life time is prolonged, repeated doses of naloxone should be administered, with a close monitoring (Chamberlain & Klein, 1994). Nalorphine is a morphine derivative acting as a morphine and other narcotics antagonist, which is used as antidote in acute morphine overdose to reverse the respiratory and CNS depression. It has no such effect in poisoning with other CNS depressants, such as barbiturates. The recommended doses are 10-20 mg IV, repeated every 15 minutes, to a maximal dose of 80 mg. Nalorphine should be cautiously administered in opiates addicted patients, because it can precipitate the withdrawal syndrome (Paul et al., 1991). After restoration of respiration and conscience, the patients must be observed and monitored with PaCO2 another 2-3 hours, before discharge (Meredith et al., 1993).

Conclusions

The main respiratory syndromes as a result of toxic exposure and overdoses are acute tracheobronchitis and laryngitis, APE, ARDS, acute chemical pneumonitis, ARF, and respiratory arrest. The substances frequently involved as cause of toxic-induced RS are

caustics, pharmaceutical agents, pesticides, CO and organic solvents. Exposure after inhalation is always followed by a RS. Combination of poisons increases the pulmonary aggression, leading to severe clinical syndromes. The outcome depends on the time of confinement in the toxic environment, time from exposure, the rapidity of the first aid and decontamination measures, as well as the early intensive care. The resuscitation protocols are of maximal importance in toxic-induced respiratory arrest. Although only 5% of poisonous substances have a specific antidote, the early recognition of the toxin involved allows the antidote administration which is mandatory for a full recovery of poisoned patients. The access of certain professionals to specific drugs must increase the vigilance in storage, manipulation, and prescription of these substances.

III.2. Life-threatening complications after intoxication with non-pharmaceutical agents

III.2.1. Cardiovascular and respiratory complications after acute exposure to pesticides and toxic gases

This direction of research is reflected in the following published articles:

1. Toma, D, Toma, TE, Bologa, C, **Lionte, C.** Unusual aetiology of a type 2 myocardial infarction: a case-based review. *Arhiv za higijenu rada i toksikologiju-archives of industrial hygiene and toxicology* 2021; 72(1): 80-87. DOI 10.2478/aiht-2021-72-3502 **(FI 1.948)**
2. Petris, OR; Bologa, C; Sorodoc, V; **Lionte, C.** Repeated Bronchoscopy - Treatment of Severe Respiratory Failure in a Fire Victim. *Journal of critical care medicine* 2017; 3(4): 162-165. DOI 10.1515/jccm-2017-0024 (ISSN 2393-1809) **Emerging Sources Citation Index (ESCI)**
3. Sorodoc L, **Lionte C**, Laba V. A rare cause of non-Q myocardial infarction-acute carbon monoxide poisoning. *Rev Med Chir Soc Med Nat Iasi*. 2004; 108(4):782-5. (ISSN: 0048-7848) **PMID: 16004217**
4. O. Petriş, F. Gradinariu, M. Totolin, J. Hurjui, M. Frasin, **C. Lionte**, C. Bologa. Sudden death in organophosphoric poisoning – an unaccountable pathophysiologic mechanism? *Rev Med Chir Soc Med Nat Iaşi.* 2004; 108(2): 325-328. (ISSN: 0048-7848). **PMID: 15688808**
5. **C. Lionte,** L. Şorodoc, V. Laba. Zinc phosphide poisoning – diagnosis, complications, treatment. *Therapeutics, Pharmacology and Clinical Toxicology* 2004; VIII (4): 87-91. (ISSN 1583-0012).
6. **C. Lionte.** Strychnine poisoning in medical practice. *Therapeutics, Pharmacology and Clinical Toxicology* 2003; VII (1): 67-74. (ISSN 1583-0012).

Background

Cardiac complications often accompany poisoning with organophosphates (OP) and toxic gases, such as CO. These may be serious and often fatal, being represented by cardiac arrhythmias, electrocardiographic abnormalities and conduction defects, as well as myocardial infarction, a rarely reported complication of acute pesticide poisoning. The extent and pathogenesis of cardiac toxicity from these compounds is not yet clearly defined. However, no guideline has included an acute poisoning as a potential cause for a type 2 myocardial infarction (MI) so far. Type 2 MI occurs as a consequence of imbalance between myocardial oxygen demand and supply and involves different mechanisms such as endothelial dysfunction of the coronary arteries, vasculitis, dysrhythmias, vasospasm, coronary embolism, severe bradyarrhythmia, respiratory failure with severe hypoxemia, severe anemia, and hypotension

or shock (Thygesen et al., 2018). Although there is no specific mention of type 2 MI in the wake of acute poisoning, MI has been reported after acute carbon monoxide (Kim et al., 2012) and organophosphate (OP) pesticide poisoning (Kidiyoor et al., 2009; Lionte et al., 2007; Kiss & Fazekas 1979; Karasu-Minareci et al., 2012), but these cases are exceptionally rare. It is known, however, that severe OP poisoning can cause direct myocardial injury (Chharba et al., 1970) and several cardiovascular complications, including ECG abnormalities, MI, impaired systolic and diastolic performance, functional remodeling, and histopathological findings (Georgidalis et al., 2018). We reported several cases who presented to our ED with life-threatening cardiovascular complications such as coma and acute non-cardiogenic APE, as a result of intentional OP ingestion, and type 2 MI after acute accidental OP ingestion in a patient with occupational exposure to OP pesticides. Initial ECG changes were asystole shortly after admission, which responded to resuscitation, followed by prolonged QTc interval, ST-T changes, right bundle branch block, and ventricular tachycardia. Finally, the development of acute MI, despite serum cholinesterase normalization resulted in death in one patient (Lionte et al., 2007). Even though we had no guidelines to fall back on, we successfully treated another patient with low-molecular-weight heparin, antiplatelets, statin, diltiazem, antidote therapy, and supportive care (Toma et al., 2021). Physicians should be aware that OP poisoning can induce type 2 MI as a complication within a few hours from exposure, and emergency management should always include close cardiac monitoring.

Smoke inhalation from all types of fires is the second leading cause of CO poisoning (Varon & Marik, 1997). CO toxicity is the result of a combination of tissue hypoxia-ischemia secondary to carboxyhemoglobin (COHb) formation and direct CO-mediated damage at a cellular level (Guzman, 2012). Cardiovascular toxic effects of CO are explained by myocardial depression as a result of hypoxic stress, cytochrome a3 dysfunction, and CO binding to cardiac myoglobin, which impairs the oxygen supply to the mitochondria, thus negatively affecting the oxidative phosphorylation and consequently, the energy source of heart muscle. Other pathogenic mechanisms are arterial hypotension (myocardial depression, NO-related peripheral vasodilatation), reduction of cerebral perfusion with loss of consciousness and ischemic reperfusion injury (Tomaszewski, 2007). The first cardiovascular manifestations after acute CO exposure are: depressed myocardial contractility (first of the right ventricle), sinus tachycardia, decreased cardiac output, pulmonary congestion and edema (hemodynamic effect and direct CO injury of pneumocytes after pulmonary cytochrome P450 inhibition), a low arterial pressure or shock, and endothelial dysfunction (Ernst & Zibrak, 1998). ECG in CO poisoning reveals repolarization changes with anterior or anterolateral topography, explained by the aggravation of a preexistent ischemia, a subclinical cardiopathy and direct effect of CO on cardiac myocytes. Arrhythmias and conduction disturbances may be recorded, and also transient patterns of acute MI, even in young patients, without cardiovascular risk factors, with normal epicardial coronary arteries (Marius-Nunez, 1990; Mokaddem et al., 2004).

Victims of domestic fire usually present with co-existing skin and respiratory lesions (Dries & Endorf, 2013; Hassan et al., 2010). In many cases, upper airway lesions are often ignored. All good medical practice reports recommend that all fire victims should be systematically evaluated by bronchoscopy (Bai et al., 2013; Mlcak et al., 2007). Criteria for bronchoscopy assessment, to standardize the severity of respiratory lesions in domestic fire cases, have been published (Jones et al., 2014). Bronchoscopy is considered to be the "gold standard" for early evaluation of upper airway injury in burns patients for predicting acute pulmonary lesions and treating these injuries (Marek et al., 2007; Bai et al., 2013). We reported the experience of using repeated bronchoscopies as a treatment tool in a case of severe respiratory failure due to bronchial obstruction by secretions and soot deposits in a domestic fire victim who associated 1-3-degree skin burns on 10% of the total body surface. Forty-eight

hours from admission, he developed severe respiratory failure, requiring repeated bronchial lavages to remove secretions and soot deposits.

We believe that admission in an intensive care unit, careful electrocardiographic and enzymatic monitoring of all patients is important for the diagnosis and treatment of cardiovascular and respiratory complications of pesticides and toxic gases. Also, daily flexible bronchoscopies and airway washings for the treatment of respiratory failure from bronchial plugs secondary to lung injury after exposure to domestic fires lesions are useful if the patient doesn't respond to treatment with mechanical ventilation alone

Materials and methods

We performed a literature review on MI in OP poisoning over the last 15 years in major databases and we revealed the main features of type 2 MI in OP poisoning. Our aim was to present diagnostic and therapeutical challenges faced by clinicians in the management of acute MI occurring as an early or late complication after exposure to OP pesticides and toxic gases. We reported a case of a woman brought by ambulance to ED one hour after accidental ingestion of an unknown quantity of a solution she used against flea infestation who developed ST segment elevation MI (STEMI) within 6 hours after admission. Another case reported was of a woman admitted to ED for an altered mental state as a consequence of CO exposure. The patient didn't experience any chest pain, but the ECG showed a non-ST segment elevation acute MI (NSTEMI), with typical rise and fall in troponin T and creatine kinase myocardial band (CK-MB) levels.

From January 2004 to December 2013, a total of 1759 cases of burnt patients were admitted to the Burns Department of Clinical Emergency County Hospital Iasi and flexible bronchoscopy was performed on all admitted patients. In most cases, mild to moderately severe lesions, graded 5 and 8 on the Jones' system of grading (Jones et al., 2013), were detected. We emphasize the experience of using multiple bronchoscopies in patients admitted for skin and respiratory lesions after exposure to toxic gases, and the need to implement a bronchial endoscopy investigation protocol for all domestic fire victims admitted to the Burns Department.

Results

Our search of articles published over the last 15 years and indexed in PubMed, Oxford Journals, Scopus, Google Academic, Science Direct, SpringerLink, and Web of Science resulted in only 11 case reports of MI following OP poisoning (Table III.11), which confirms that this is a rare occurrence. MI can occur within hours or days after acute OP exposure. Two articles report type 1 MI early after OP exposure (Table III.11). One report (Joshi et al., 2013) refers to a patient poisoned with OP who presented with out-of-hospital cardiac arrest. This patient was successfully resuscitated, the initial ECG showed inferolateral ST segment elevation (possible after defibrillation), although no coronary artery lesions were documented and no troponin elevation recorded. This patient does not meet the criteria for diagnosing MI (Thygesen et al., 2018). Another paper (Kidiyoor et al., 2009) refers to MI occurring seven days after parathion ingestion (based on the TTE and troponin and CKMB levels), but coronary angiography revealed a 20 % stenosis of the left anterior descending coronary artery consistent with patient's known history of diabetes, and there is no mention of ECG. Because of such a delay between OP poisoning and MI, we think that the two acute events are associated rather than causally related (Höfler, 2005). Finally, one paper (Ayyadurai et al., 2018) reported STEMI shortly after OP exposure in a young patient, with patent coronary arteries on angiography, which might suggest type 2 MI, but it does not mention occupational exposure to OP.

Table III.1 Case reports of myocardial infarction following organophosphate poisoning

Year	Authors	Time*	Type of poisoning	Type of MI	Coronary angiogram	Outcome
2018	Tkaczyk Jędrzej et al.	24 h	Intentional	Type 1	3-vessel disease	Dead
2012	Karasu-Minareci et al.	1-2 h	Accidental	Type 1	90 % RCA stenosis	Recovered
2018	Ayyadurai et al.	UA	Intentional	Type 2	Patent coronaries	Recovered
2009	Kidiyoor et al.	7 days	Intentional	Type 2	LAD 20 % obstruction	Dead**
2017	Kuo et al.	2nd night	NS	Inferolateral STEMI	No lesions	Dead
2014	Pankaj et al.	5 days	NS	STEMI	Postponed	Recovered
2013	Joshi et al.	2 days	Intentional	STEMI	NP	Recovered
2014	Aydın et al.	UA	Accidental	STEMI	NS	Recovered
2014	Kumar et al.	3 days	Intentional	Inferolateral STEMI	NP	NS
2010	Mdaghri et al.	20 h	NS	Endocardial ischaemia	NS	Dead
2007	Lionte et al.	24 h	Intentional	Anteroseptal STEMI	NP	Dead**

*, after admission; MI, myocardial infarction; h, hours; RCA, right coronary artery; UA, upon admission; LAD, left anterior descendent coronary artery; **, autopsy confirmed diagnosis; NS, not specified; NP, not performed.

We reported the case of a 61-year-old woman who was brought to the ED by ambulance one hour after accidental ingestion of an unknown quantity of OP solution from a bottle she confused for a drink. She came from a rural area where she had worked in agriculture and had been occupationally exposed to OP, carbamate, and organochlorine pesticides through inhalation and skin contact for 10 years. She had a history of surgery for post-traumatic subdural hematoma three years before the accident, without other known cardiovascular risk factors. She presented with clinical signs and symptoms of dizziness, myosis, excessive sweating, hypersalivation, sphincteric incontinence, muscle fasciculation, tremor of the extremities, pale skin, and alcoholic and pesticide breath odor. Her Glasgow Coma Scale was 9, and she was uncooperative, which made taking clinical history very difficult. Her initial blood pressure was 200/100 mmHg, and the first ECG in the ED showed narrow QRS-complex tachycardia with a heart rate of 122/min. Arterial blood gas analysis revealed lactic acidosis (pH 7.26), lactate 6.3 mmol/L, bicarbonate 18.8 mmol/L, potassium 2.5 mmol/L, calcium 1.05 mmol/L. Laboratory findings detected leukocytosis ($16.93x10^3$ /µL), neutrophilia ($13.9x10^3$ /µL), hyperglycemia (12.71 mmol/L), and an ethanol level of 215 mg/dL. Relative reference ranges of our laboratory are: white blood cells $4–10x10^3$ /µL, neutrophils $2–8x10^3$ /µL, glucose 4.55–5.55 mmol/L, and ethanol < 10 mg/dL. Cardiac markers were also elevated upon ED admission: creatine kinase (CK) was 412 U/L (reference range 20–170 U/L), CK-MB 73 U/L (ref. range 2–25 U/L), lactate dehydrogenase (LDH) 292 U/L (ref. range 135–214 U/L), N-terminal pro-brain natriuretic peptide (NT-proBNP) 524 pg/mL, cardiac troponin I (cTnI) 1.75 ng/mL (ref. range 0–0.02 ng/mL), and GOT 32 U/L (ref. range 5–32 U/L). The plasma cholinesterase level was 279 U/L (range 5320–12920 U/L). Other biological parameters were within normal ranges. These findings pointed to acute OP pesticide poisoning (based on muscarinic and nicotinic signs and symptoms), and treatment was immediately started in the ED with oxygen therapy face mask (4 L/min), IV antidote (combining 2 mg atropine and the initial bolus of 250 mg obidoxime), and gastric lavage. The patient was then transferred to a medical ward, where she regained full consciousness and became cooperative. Physical examination one hour after ED admission established 150/100 mmHg blood pressure, 122/min heart rate, and mydriatic pupils. She had

a body mass index of 24.4 kg/ m^2, she denied smoking, and declared occasional alcohol drinking. ECG showed ST segment depression in leads V3-V4, T flat in D1, aVL, V5-V6, but no signs of hypokalemia (Figure III.9).

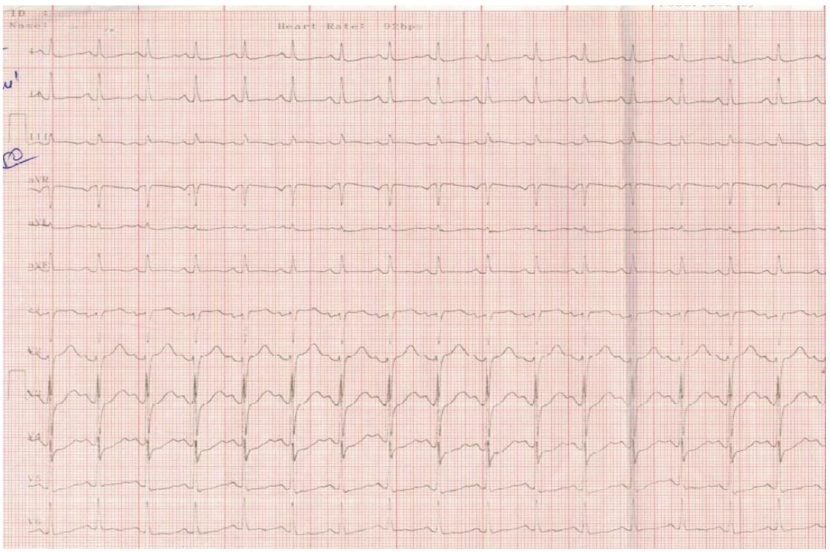


Figure III.9. ECG upon ED admission

Antidote therapy continued with 1 mg atropine every hour (with reassessment of heart rate and pupil diameter every 15 min) and slow continuous IV obidoxime administration (1 g/24 h), combined with diazepam (5 mg), which led to resolution of the muscarinic signs and muscle fasciculations within three hours of first antidote administration. Transthoracic echocardiography (TTE) in the medical ward showed 48 % ejection fraction of the left ventricle (LVEF), 24 % fractional shortening (FS), calcification of the aortic knob, no valve lesion, and no segmental wall motion abnormalities or thrombi.

Clinical observation continued hourly and showed mydriatic pupils. Paraclinical parameters were also monitored, and hydro-electrolyte correction was continued. Careful atropine administration also continued to control muscarinic signs and symptoms because of the initial sinus tachycardia. Six hours after the initial assessment at the ED, cardiac enzymes and biomarkers were as follows: cTnI 2.89 ng/mL, NT-proBNP 1314 pg/mL, CK 1389 U/L, CK-MB 104 U/L, TGO 89U/L, and LDH 354 U/L. At 28 h, their values peaked to cTnI 6.84 ng/mL, NT-proBNP 14,774 pg/mL, CK 2614 U/L, CK-MB 125 U/L, TGO 148 U/L, and LDH 484 U/L. ECG monitoring showed sinus tachycardia and important ST segment elevation >1 mm in DII, DIII, aVF, with ST depression in aVL, flat T waves in V5, and negative T waves in V6 (Figure III.10). All this confirmed the diagnosis of STEMI.

Therapy with low-molecular-weight heparin (enoxaparin), antiplatelets (aspirin, clopidogrel), and a statin was initiated immediately, while antidote therapy continued. The patient was transferred to the Cardiology Department, where ECG showed an inferior STEMI and supraventricular tachycardia. LVEF was at 46 %, one third of the basal inferolateral and inferior walls were hypokinetic, one third of the basal anterior interventricular septum dyskinetic, and the aortic valve was calcified. Emergency coronarography showed normal epicardial coronary arteries with no obvious stenotic artery or thrombosis (but a confirmation test of coronary vasospasm was not performed). All this confirmed the diagnosis of type 2 acute inferior STEMI with normal epicardial coronary arteries.

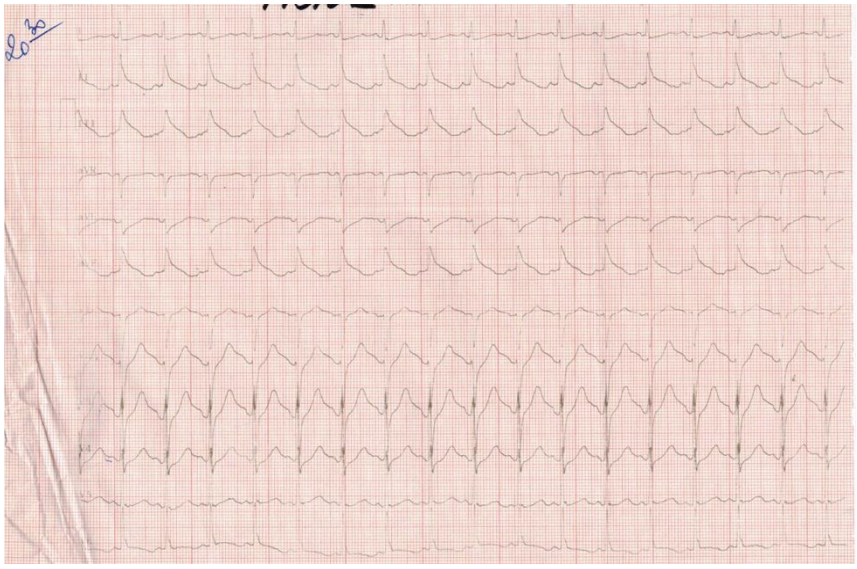


Figure III.10. ECG 26 hours after admission

Therapy continued in the Coronary Critical Care Unit (CCU) with triple antithrombotic therapy, diltiazem, statin, and continued antidote administration and supportive care. After development of MI, atropine was administered cautiously for the next 2 days, when myosis and signs of exocrine gland hypersecretion appeared. 48 hours after coronary angiography, the patient developed acute renal failure (creatinine 2.15 mg/dL, BUN 87 mg/dL), possibly after contrast substance administration, which was successfully addressed in the Cardiology Department. She was transferred back to our department to complete the medical treatment of MI, OP poisoning, and its complications. For three days she received two units of human plasma a day for exogenous pseudocholinesterase supply, because her level of cholinesterase remained low (1,568 U/L) despite obidoxime administration for 72 hours since poisoning. Systolic blood pressure remained below 110 mmHg, allowing only a low dose of ramipril as part of the medical treatment of MI. Also, a short episode of nonsustained ventricular tachycardia occurred during CCU stay, which was resolved with lidocaine bolus followed by a 24-hour infusion. During hospitalization, the patient developed left inferior lobe pneumonia due to infection with Klebsiella pneumoniae, which was treated with ciprofloxacin, mucolytics, and expectorants. Renal function returned to normal, and metabolic and electrolyte derangements were all corrected. The level of HbA1c and fasting glucose were also normal, which ruled out diabetes as a cardiovascular risk factor. The patient was discharged in good condition after 11 days, with ECG showing persistent ischemic changes in the infero-lateral territory (Figure III.11) Cardiac enzymes, liver and renal function, and plasma cholinesterase (5463 U/L) were normal.

Our case is particular inasmuch as our patient had no cardiovascular risk factors, had been occupationally exposed to pesticides for 10 years, and developed type 2 STEMI within six hours of accidental ingestion. To the best of our knowledge, this is the first case of an acute type 2 MI following accidental poisoning with OP in a patient with chronic occupational exposure to OP pesticides.

Another report is about a 77 years-old woman admitted for somnolence, slurred speech, obtundation, disorientation, ataxia. She was found unconscious at home, in the cellar where were barrels with wine in fermentation process. The son, who saved her, also reported dizziness and headache after entering the cellar. After breathing fresh air, the patient becomes partially cooperative, but obtunded. Past medical history was unremarkable, except for occasional alcohol intake. Physical examination reveals altered general condition, pallor, BP 130/70

mmHg, tachycardia 110 bpm, hepatomegaly 2 cm below the ribs cage. ECG upon admission shows sinus tachycardia.

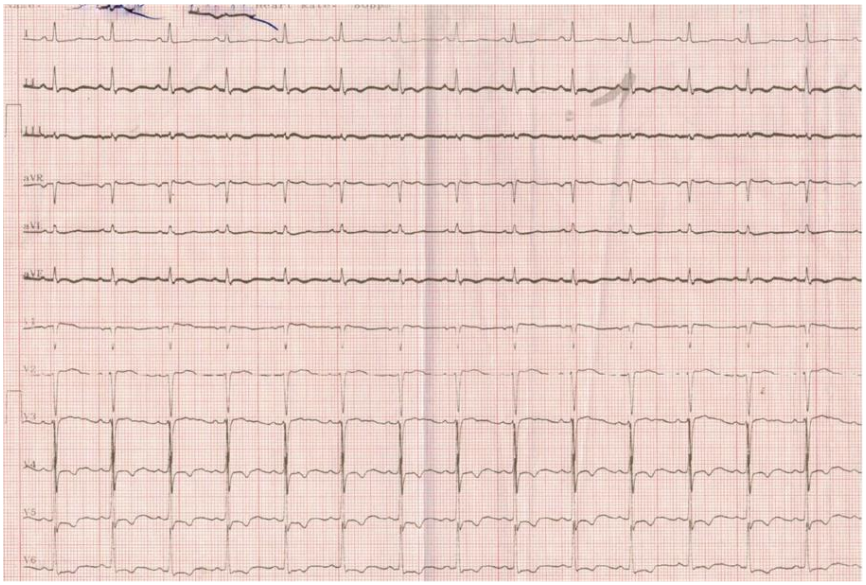
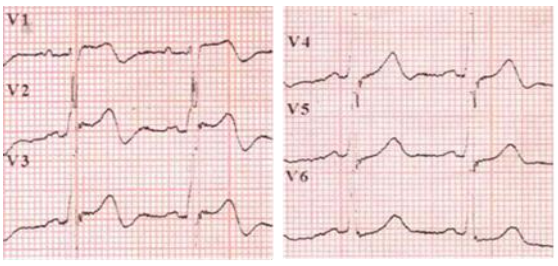
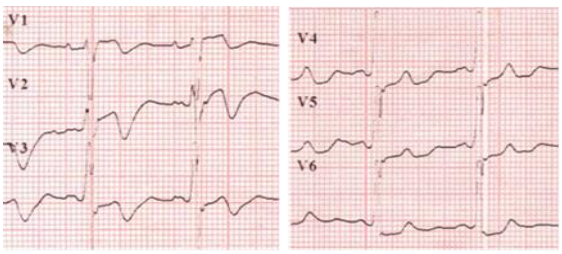


Figure III.11. ECG before discharge

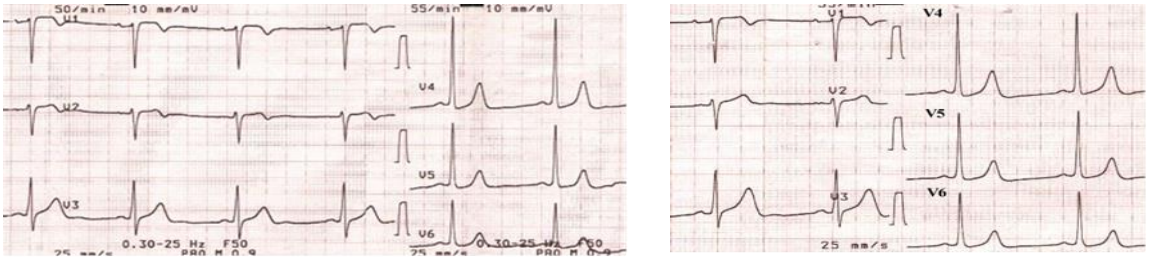
Laboratory tests confirmed the CO poisoning (CoHb level 20%), and showed leukocytosis 16,000/mmc with neutrophilia 91.3%, increased blood glucose of 103 mg/dL, BUN 76.8 mg/dL, creatinine 1.3 mg/dL, AST 95 U/L, ALT 62 U/L, LDH 612 U/L, with normal Hb, electrolytes, CK and CKMB. Oxygen therapy on nasal canula 6l/min is administered, together with supportive therapy, followed by an improvement of her condition. 24 hours after admission, the BP drops to 80/50 mmHg, and ECG changes are revealed (Figure III.12): first a ST segment elevation with diphasic T waves in V1-V3, without chest discomfort. Laboratory investigations revealed increasing levels of AST 295 U/L, ALT 192 U/L, LDH 1,212 U/L, and an elevation of CK 1,486 U/L, CK-MB 90 U/L and troponin T 1.5 ng/ml. TTE showed hypokinesia of the basal segments of LV anterior wall and interventricular septum (IVS). A diagnosis of NSTEMI was made based on ECG and biomarkers' dynamic, and imagistic criteria. The therapy for acute coronary syndrome was immediately initiated, using LMWH, betablockers, calcium-channel blockers, antiplatelets, statin, leading to a favorable outcome, with a good clinical and ECG evolution (Figure III.12) and normalization of cardiac enzymes seven days after admission. Patient was discharged fully recovered, with an indication for coronary angiography.



a. 24 hours after admission.



b. 48 hours after admission.



c. Five days from admission. d. Ten days after admission.

Figure III.12. The evolution of ECG changes during hospitalization.

We emphasized the importance of using repeated bronchoscopy in the management of ARF after exposure to toxic gases and fumes, in the report about a 23-year-old man, victim of a closed space house fire, who was admitted to the Emergency County Clinic Hospital Iasi, Romania 48 hours after exposure. On admission, the physical examination revealed an overweight patient with a BMI of 28.7 kg/m2, with 1-3-degree skin burns on 10% of the total body surface involving areas of the face, left shoulder, arm and forearm, and both hands. He was conscious and hemodynamically stable. He had dyspnea with polypnea (25 breaths/min), productive cough with yellow grey sputum, and bilateral rhonchi were detected on pulmonary auscultation. Chest X-rays revealed an area of pulmonary condensation in the superior lobe of the left lung, while the right lung area appeared radiologically normal. Arterial blood gases (ABG) analysis while breathing room air showed pO2 120 mmHg, pCO2 60 mmHg, SaO2 94%, pH 7.32. Laboratory tests showed marked leukocytosis (34,100/mmc) with neutrophilia, increased AST (73 U/l), CK (1,868 U/l) and LDH (1,161 U/l), increased lactate level (1.3 mmol/l), and glycemia 119 mg/dl.

Forty-eight hours after admission, despite receiving supplemental oxygen via nasal cannula, the patient progressively developed severe dyspnea and tachypnea with a respiratory rate of 32/minute, peripheral cyanosis and agitation, tachycardia (134/min), low blood pressure (80/40 mmHg) and decreased oxygen saturation (70%). ABG showed pO2, 41 mmHg; pCO2, 98 mmHg; pH = 7.18, and PaO2/FiO2 = 102, which were consistent with the diagnosis of ARF. The patient was promptly intubated and mechanically ventilated. A bedside chest X-ray showed bilateral confluent multiple nodular lesions similar to those described in moderate ARDS. Despite repeated attempts to correct ventilation, only a limited improvement of arterial gases was achieved. Mechanical ventilation using BiPAP mode with FiO2 100% which was progressively increased 5 to 7 cm water PEEP improved the oxygen saturation to 86% and pO2 to 54 mmHg. The change of inspiratory pressure (Pi) from 25 to 35 cm water failed to improve the tidal volume, which remained at 350 ml. It was considered necessary to increase the respiratory rate to 16-18 breaths/min to correct hypoventilation and to decrease pCO2. At this point, it was suspected that an obstruction of the superior airway had occurred, and an emergency endoscopy was requested. This showed a grade 2 inhalation injury, numerous white-grey secretions and soot deposits which had formed bronchial casts causing severe airway obstruction (Figure III.13).

The removal of the bronchial casts required the use of biopsy forceps to detach the pseudo membranes and when completed, revealed a normal bronchial mucosa underneath. The respiratory status of the patient, as well as the parameters of arterial blood gases, improved after daily bronchial endoscopic lavages. Bronchoscopy was necessary for eight days to clean all bronchial secretions and soot deposits efficiently. Extubation was possible ten days after the development of the severe respiratory failure.

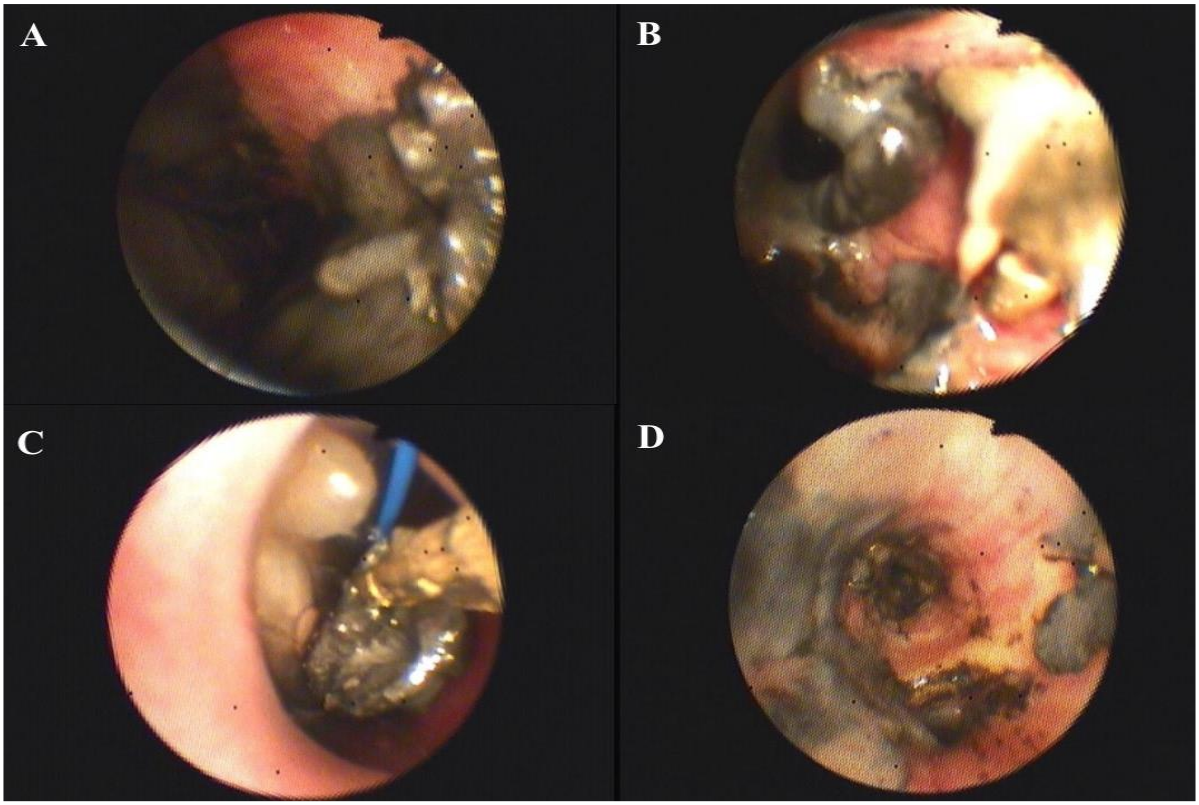


Figure III.13. Endoscopic appearance of the airways
A. Secretions and deposits of soot; B. Organized bronchial casts; C. Removal using bronchial forceps; D. Revealing a normal bronchial mucosa underneath the secretions.

The serial direct microscopic exam of the samples collected daily revealed an inflammatory reaction, with neutrophils and fibrin. No bacterial growths were obtained from repeated culture of broncho alveolar specimens. The skin burns and lesions of the upper airway responded favorably to supportive therapy, broad spectrum antibiotherapy and analgesia with remifentanil 0.075-1 mcg/kg/min, continuous infusion for 8 days. The bronchoscopy performed just before discharge revealed no secretions, no luminal obstructions and no fistulas. The patient was released from the hospital after 24 days.

Discussion

Type 2 MI is a heterogeneous syndrome, which can be primary or secondary illness and is caused by either acute non-atherothrombotic coronary artery disease or other acute noncoronary trigger/illness (Sandoval et al., 2020). However, the European or American STEMI guidelines (Ibanez et al., 2017; Antman et al., 2004) make no mention of acute poisoning (e.g., CO, OP, or cyanide poisoning) as possible cause. OP poisoning can be followed by cardiovascular complications (Lionte et al., 2007) within the first few hours. By inhibiting acetylcholinesterase irreversibly, OP pesticides can cause acetylcholine to accumulate and overstimulate cholinergic synapses in the CNS. They can also cause heart dysrhythmia, hypertension, or hypotension (Kiss & Fazekas 1979; Karasu-Minareci et al., 2012). The distinct features of OP poisoning include prolonged PQ and QT intervals (responsible for ventricular arrhythmia and ventricular fibrillation), ST-T changes, AV block, and bradycardia (Karki et al., 2004; Lionte et al., 2012). Cardiac toxicity starts with a brief period of increased sympathetic tone followed by prolonged parasympathetic hyperactivity, hypoxemia, acidosis, electrolyte derangements, and a direct toxic effect on the myocardium

(Ludomirsky et al., 1982; Karki et al., 2004). In addition, QT prolongation may be followed by torsade de pointes ventricular tachycardia and ventricular fibrillation (Karki et al., 2004). Also, bundle branch block may be documented (Lionte et al., 2007) Parasympathetic hyperactivity plays a major role in the coronary artery spasm, which is an important factor in the pathogenesis of type 2 MI (Thygesen et al., 2018; Lionte et al., 2012). Pesticides can increase the amount of catecholamines and other vasoactive amines, which can cause coronary thrombosis or spasm and eventually lead to myocardial infarction (Kumar et al., 2014).

Anand et al, 2009 examined cardiac abnormality in acute OP poisoning and revealed that there were cardiac discoloration or blotchiness, patchy pericarditis, auricular thrombus, right ventricular hypertrophy, myocardial interstitial edema, vascular congestion, patchy interstitial inflammation and mural thrombus.

As the changes in serum cholinesterase activities were involved in the pathogenesis of MI secondary to pesticide poisoning, acetylcholinesterase and butyrylcholinesterase can serve as diagnostic markers for the parasympathetic/sympathetic balance and can predict cardiovascular adverse events. About one third of severely poisoned patients have elevated troponin I levels, indicative of MI, and ST depression and/or elevation are more common in patients with elevated TnI (Waiskopf et al., 2016). When there is a short interval (hours) after an acute exposure to OP, the relationship between the two situations is likely causal, and the arguments are clearly demonstrated in literature (Peter et al., 2014; Cha et al., 2014). A study which analyzed pesticide use and MI incidence among farm women (Dayton et al., 2010) revealed an increased risk of MI associated with low-level pesticide exposure in women. This might explain the occurrence of type 2 MI in our patient within six hours of accidental ingestion of an OP pesticide solution. Patients classified as having a type 2 MI were older, more often female, with more comorbidities, and a lower peak in cTnI (DeFilippis et al, 2019). This was the case with our patient too.

The therapy of the type 2 MI in OP poisoning needs a separate discussion, since there are no specific recommendations in the STEMI guidelines (Ibanez et al., 2017; Antman et al., 2004) for this etiology of MI. Given that we blamed coronary vasospasm for the infarction, we chose diltiazem over a beta-blocker for the treatment. Close monitoring of ECG changes in the ED and later on is very important and can require further treatment, including antidote administration and supportive care (Tamis-Holland et al., 2019; Sundagaragiri & Tandur, 2016).

Patients with type 2 MI have higher short- and long-term mortality than those with type 1 MI (Waiskopf et al., 2016), and in-hospital mortality rates are 2–3 times higher than those reported for type 1 MI because of non-cardiovascular events (Putot et al., 2018). A recent study (Padney et al., 2020) tested a hypothesis that rise in cardiac troponin T (cTnT) and CK-MB follows a different pattern between type 1 and type 2 MI and that the ratio of cTnT to CK-MB is disproportionately higher in type 2 than type 1 MI. It concluded that patients with marked elevations in these biomarkers may be more likely to have type 1 MI, whereas those with mildly elevated CK-MB and moderately elevated cTnI may be more likely to have type 2 MI, which was also the case with our patient. Studies regarding the outcome of pesticide related MI showed that significantly associated with non-fatal MI were chlorpyrifos, coumaphos, carbofuran, metalaxyl, pendimethalin, trifluralin, Aldrin, DDT, and 2,4,5-Trichlorophenoxyacetic acid which all had odds ratios greater than 1.2 whereas Ethylene dibromide, Mancozeb, Ziram and Chlorophenoxy herbicides were significantly associated with MI mortality with odds ratios ranging from 1.2 to 2.4 (Wahab et al., 2016).

In patients exposed to toxic gases such as CO, the occurrence of MI is favored by generalized tissue hypoxia, direct CO toxic effect on myocardial mitochondria, with perturbation of cell metabolism, to which contributes inadequate myocardial perfusion,

increase tendency to thrombosis, coronary vasospasm with or without coronary thrombosis, and in elderly patients, preexistent coronary lesions (Fiorista et al., 1993; Marius-Nunez, 1990). Ultrastructural and functional studies in acute CO poisoning demonstrated the presence of glycogen deposits near abnormal mitochondria, as an expression of incapacity of mitochondria to use the energy substrate, in the setting of a normal myocardial perfusion, suggestive for stunned myocardium (Tritapepe et al, 1998). Scintigraphy changes in acute CO poisoning showed either myocardial necrosis, transient ischemia, or stunned and hibernating myocardium (Pach et al., 2001). The patients poisoned with CO who have COHb level > 5% and transmural MI have a more severe evolution, a high risk for arrhythmias, and higher levels of CK compared with patients with non-Q MI (Elsasser et al., 1995). The prevalence of medical complications and deaths in this poisoning is significant in elders, which recover fully after poisoning only in 28.4% cases (Targosz & Pach, 2002).

As reported in the literature on domestic fire victims with inhalational smoke injuries, upper airway lesions are often ignored. Pulmonary lesions usually cause problems which commence a few days following the fire and lead to worsening of the patient's vital prognosis. Serial bronchoscopies with lavage have been reported to be useful for clearing of mucus plugs (Traber et al., 2007; Enkhbaatar & Traber, 2004; Lee & Mellins, 2006). There are contradictory opinions regarding serial fiberoptic bronchoscopies in patients with smoke inhalational injuries, because of the lack of prospective or interventional studies (Amin et al, 2015). However, a study performed on 624 patients with smoke inhalational injuries showed a trend toward shorter hospitalization in patients who underwent more than one bronchoscopy procedure (Carr et al., 2009). There are multiple causes, in addition to smoke inhalation, which contribute to lung injury, such as systemic inflammation in response to burns, ventilator-induced injury or pulmonary infections (Dries & Endorf, 2013).

Scoring systems have been formulated to identify patients with a poor prognosis after inhalation of toxic gases and fumes. The Abbreviated Injury Score grading scale is one of them and is correlated with increased mortality in burn victims (Walker et al., 2015). There are two types of respiratory injuries that appear in domestic fire victims, injuries related to smoke inhalation and injuries related to the heat generated by a fire (Dries & Endorf, 2013; Lee & Mellins, 2006). Patients with respiratory injuries have a poor prognosis and a mortality rate of up to 20%. When there are associated pulmonary infections, the mortality rate can reach 40% (Dries & Endorf, 2013; Enkhbaatar & Traber, 2004).

Conclusions

MI following OP and CO acute poisoning is a rarely reported complication and clinicians should be aware of this early complication to assess all cardiac biomarkers as soon as a patient is admitted to ED. Also, cardiac monitoring after OP or CO acute exposure of all patients, irrespective of their age, is mandatory to be able to diagnose such an event. Even though no guidelines are available to date, our opinion is that treatment with low-molecular-weight heparin, antiplatelets, statin, diltiazem, ACE inhibitors, along with antidote therapy, and supportive care is mandatory in this situation. We hope that the existing MI guidelines should include evidence-based specific treatment for these toxicological emergencies. This might improve the outcome and prevent fatalities.

Daily flexible bronchoscopies and airway washings for the treatment of respiratory failure from bronchial plugs secondary to lung injury after exposure to domestic fires lesions contributes to recovery of patients unresponsive to treatment with mechanical ventilation alone.

III.2.2. Hepatotoxicity and metabolic disturbances after exposure to solvents

This direction of research is reflected in the following published articles:

1. **Lionte, C.** Lethal complications after poisoning with chloroform - case report and literature review. *Hum & Exp Toxicol.* 2010; 29(7): 615-622 DOI: 10.1177/0960327109357142 (ISSN: 0960-3271) (**FI 1.211**)
2. **C. Lionte**, L. Şorodoc, Victoriţa Laba, J. Hurjui. The effect of ethanol on blood glucose in acute and chronic poisoning. *Curierul Medical (Chişinău)* 2005; 1 (283): 21-27. ISSN: 0130-1535.
3. **C. Lionte**, L. Şorodoc, Victoriţa Laba. Alcoholic hypoglycemia in medical practice. *Therapeutics, Pharmacology and Clinical Toxicology* 2004; VIII (4): 80-86. (ISSN 1583-0012).

Background

Chloroform is a potent central nervous system and respiratory depressant. The toxicities associated with chloroform frequently occur after inhalation. Chloroform is an ubiquitous atmospheric and water contaminant (Gemma et al., 2003). From its introduction in 1847 as a potent anesthetic agent, until its decline in clinical use in 1976, incidence of hepatic failure after chloroform inhalation was reported to be between 1 in 25,800 and 1 in 51,700 cases (Wawersik, 1997; Elliot & Strunin, 1993). Hepatotoxicity after chloroform exposure is secondary to production of a toxic metabolite, with a peak elevation of liver enzymes 72 hours after exposure. Acute liver failure (ALF) after chloroform inhalation is rarely described, this syndrome being produced mainly by viral hepatitis, idiosyncratic drug-induced liver injury, and acetaminophen ingestion. ALF is a clinical syndrome resulting from massive necrosis of the liver cells or sudden and severe impairment of liver function (Sherlock & Dooley, 1993), which can be produced by several predictable hepatotoxins, such as carbon tetrachloride and chloroform (Kaplowitz, 2004; Navarro & Senior, 2006). Rhabdomyolysis (meaning destruction of striated muscle) results in the leakage of the intracellular muscle constituents into the circulation and extracellular fluid (Farmer, 1997; Warren et al., 2002). Rhabdomyolysis can be a life-threatening condition associated with extreme elevations in CK, electrolyte imbalances, acute kidney injury (AKI), and DIC (Gabow et al., 1982).

Ethanol is the foremost rhabdomyolysis-inducing agent, because it has a toxic effect on myocytes and a depressant effect on the CNS, which leads to periods of prolonged immobility (Criddle, 2003). Ethanol ingestion might produce either a hyperglycemia, or a hypoglycemia. Alcohol addiction is one of the most frequent causes of hypoglycemia, in relation with a high frequency of alcohol intake. Hypoglycemia occurs not only in chronic alcoholics, but also in occasional drinkers (Belis, 1988).

Aim of the research

The current concepts on liver toxic effect of chloroform and alcohol, as well as acute chloroform poisoning are reviewed. The evaluation of ethylic alcohol effect on blood glucose in acute and chronic poisoning in non-diabetic patients and the metabolic changes in acute alcoholic hepatitis were studied, leading to practical conclusions to provide an efficient management of these patients referred to medical specialties (internal medicine, gastroenterology, emergency medicine and family medicine).

Materials and methods

A literature review of reported complications after chloroform acute poisoning and/or chronic exposure was presented, along with a case of a 46-year-old woman who presented to

ED with coma, signs of respiratory failure, and solvent odor of her breath after chloroform inhalation and binge drinking. The patient died as a result of lethal ALF and rhabdomyolysis, despite maximum supportive care. Pathology examination revealed micro vesicular steatosis and tubular renal necrosis, specific for chloroform toxicity. Mechanisms of chloroform and alcohol-induced liver toxicity were reviewed.

A prospective study on blood glucose changes in patients admitted in the Internal Medicine department with acute and chronic ethanol poisoning, over an 18-month period, regardless of clinical severity (i.e., acute drunkenness, alcoholic coma) was performed. We had a control group, which consisted of admitted patients with a diagnosis of chronic alcoholic hepatitis, and alcohol addiction, which were similarly investigated. Also, patients admitted only in ED with acute ethanol poisoning were included. Patients who did not cooperate for oral glucose tolerance test (OGTT), those with an endocrinological of functional cause for hypoglycemia or those who received glucose upon transportation to hospital, and patients who didn't sign an informed consent were excluded from the study. Biochemical evaluation consisted of repeated determination of blood glucose, a prolonged 6 hours-OGTT within 24 hours from admission, liver function tests, and toxicological exams. Statistical significance of the differences between the groups analyzed was assessed with t Student's test and Chi-square (for categorical variables, or testing the hypothesis). A p value < 0.05 was considered significant.

Results and discussion

Chloroform (trichloromethane, $CHCl_3$) is a colorless, volatile liquid with a pleasant ethereal odor (Deshon, 1979). Although negligible amounts of chloroform may be produced naturally in the atmosphere and in soil and water (Clayton & Clayton, 1981), manufacturing is the main source. Chloroform is the main trihalomethane generated during the chlorination of drinking water, and is widely used as an intermediate in the production of refrigerants, pharmaceuticals, and as a general solvent (Meredith & Vale, 1983).

The most frequent and important route of entry for human exposure to chloroform is inhalation. Poisoning by this route was best understood from experience of its use as a general anesthetic. Up to 64%–67% of chloroform from inspired air is retained in the body. Pulmonary intake is directly related to the chloroform concentration in the air, the ventilation volume, and the duration of exposure (Brown et al., 1974). The primary sites of P450-mediated metabolism are the liver and kidneys. Chloroform is metabolized by oxidative dehydrochlorination of its carbon– hydrogen bond to form phosgene (CCl_2O), carbine, and chlorine (Figure III.14). At low levels, $CHCl_3$ is metabolized primarily to phosgene by CYP2E1 (high affinity – low-capacity enzyme). When the CYP2E1- mediated reaction is saturated, the predominant role in phosgene production is for CYP2A6, efficient even in highly hypoxic conditions and only at high substrate concentrations (Gemma et al., 2003). The reactive metabolites are prevented from covalently binding to microsomal proteins by hepatic glutathione (GSH). Phosgene depletes hepatocellular GSH. The hepatotoxicity of chloroform is related to the rate of biotransformation into its active metabolites and the availability of GSH to mop up these metabolites. Also, it has been suggested that chloroform has a direct effect on the hepatic microsomal calcium pump necrosis (Moore, 1980; Plaa, 2000). Chloroform is a classic model of liver injury. Hepatocellular steatosis and necrosis are features of the acute lesion; steatosis is explained by the up-regulation of CYP2E1. Mitochondria and the endoplasmic reticulum are target sites (Patrick, 2002; Wawersik, 1997).

The major end product of chloroform metabolism is carbon dioxide (CO_2), most of which is eliminated via the lungs, but some is incorporated into endogenous metabolites and may be excreted as bicarbonate, urea, methionine, and other amino-acids (Deshon, 1979).

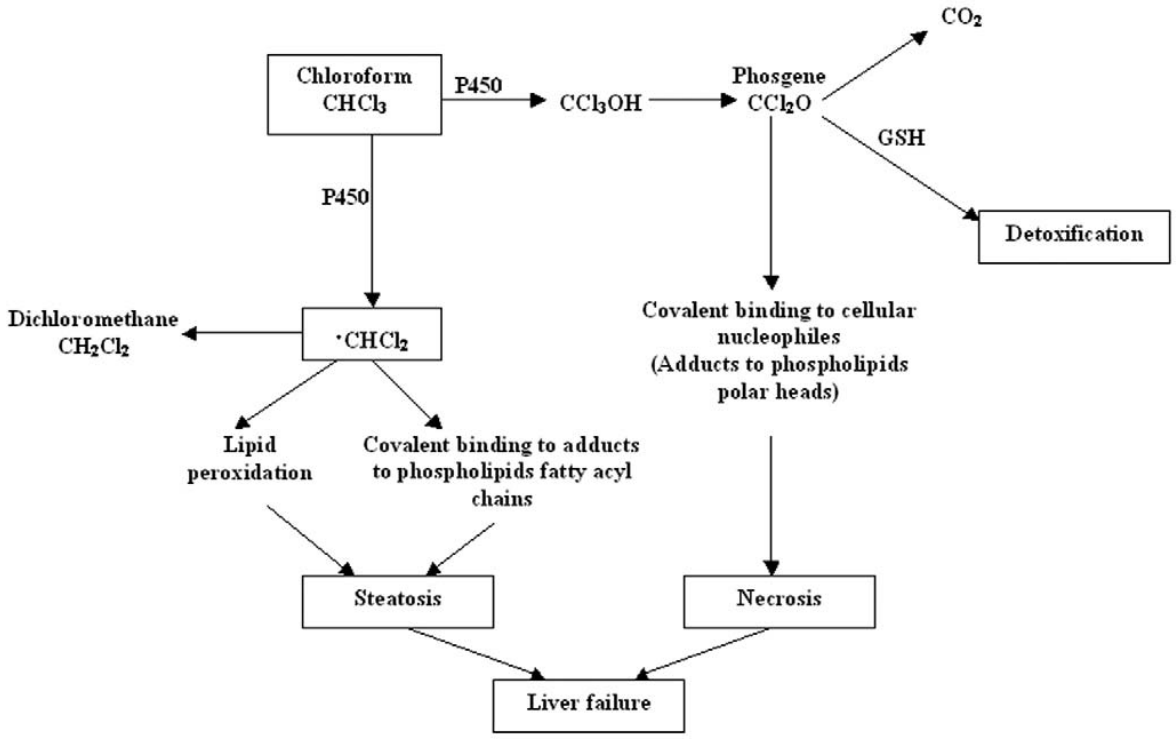


Figure III.14. Chloroform (CHCl3) bioactivation and mechanism of liver injury.
GSH, reduced glutathione; GSSG, oxidized glutathione; P450, cytochrome P450; CCl2O, phosgene

Excretion of chloroform occurs primarily via the lungs, either as unchanged chloroform or as CO2 (Brown et al., 1974). Target organs for chloroform toxicity are CNS, the liver, and kidneys. Chloroform is a respiratory and CNS depressant, inducing narcosis and anesthesia at high concentrations (Storms, 1973).

The signs and symptoms of CNS and respiratory depression, solvent odor, and delayed liver toxicity are highly suggestive of chloroform intoxication (Table III.12). Chloroform is acutely toxic to the liver although damage may not be fully apparent in the first 12–48 hours after exposure. Liver effects include centrilobular necrosis and reduced prothrombin formation (Meredith & Vale, 1983).

Acute chloroform exposure may result in death by respiratory failure, acute cardiac failure, and centrilobular liver necroses (Meichsner et al., 1998; Kim et al., 1996). A literature review of reported complications after chloroform acute poisoning and/or chronic exposure is presented in Table I.1.2.2.2.

Alcohol potentiates chloroform-induced liver injury because it produces enzyme induction, which increases the rate of metabolism. Other predisposing factors are hypoxia, hypercapnia, dehydration, and acidosis (Thorpe & Spence, 1997; Kasai et al., 2002). In the case reported, predisposing factors for chloroform-induced liver injury were ingestion of ethanol, hypoxia, hypercapnia, acidosis (secondary to respiratory depression), and chronic alcoholism. Alcoholic liver disease (ALD) is one of the major medical complications of alcohol abuse. Factors increasing susceptibility to ALD in this patient were represented by the patient's sex (female), fasting, binge drinking, lifetime intake of alcohol, and high concentration of alcoholic drinks. The three most widely recognized forms of ALD are alcoholic steatosis, in at least 80% of heavy drinkers, acute alcoholic hepatitis, and cirrhosis (Walsh & Graeme, 2000).

Table III.12. Clinical effects of acute poisoning with chloroform (reproduced from Lionte, 2010)

	Clinical and biological findings	Mechanism
Cardiovascular	Arrhythmias – ventricular fibrillation; hypotension	Direct effect on the myocardium, decrease in parasympathetic activity, increase in adrenergic sensitivity, altered ion homeostasis, altered coronary blood flow; decreased contractile power of myocardium and peripheral vasodilatation arising from vagal stimulation
Respiratory	Respiratory failure	Paralysis of the medullar respiratory center
CNS	Coma, convulsions, and sudden death	Depression of the CNS, paralysis of the respiratory center
Autonomic nervous system	Dilatation of pupils, nausea, vomiting, salivation and profuse sweating	Vagal stimulation
Gastrointestinal (after ingestion)	Irritation and burns of the gastrointestinal mucosa, vomiting, diarrhea	Vagal stimulation or a direct local action
Hepatic	High serum bilirubin and transaminases, deficiency of prothrombin and fibrinogen	Necrosis of liver cells, with hepatic failure
Renal	Oliguria	Damage to the renal tubules, mainly involving the epithelium of Henle's loop
Hematological	Hemorrhages	Damage of the erythrocyte membrane; impaired blood clotting by deficiency of prothrombin and fibrinogen
Metabolic	Acid-base disturbances, fluid and electrolyte disturbances	Secondary to respiratory failure, vomiting and diarrhea

Fatty alcoholic liver is less often morphologically characterized by micro-vesicular steatosis (Sherlock & Dooley, 1993). Deaths due directly to fatty liver are rare and are usually caused by ALF or fat embolism (Walsh & Graeme, 2000). In this case, steatosis can be a consequence of alcohol intake, but doesn't explain the ALF that has led to death. Chronic alcohol consumption in this patient not only produced an ALD, revealed by history of recent alcohol binge drinking, a detectable serum alcohol level, and AST level greater than that of ALT by a ratio >2:1, but also enhanced the hepatotoxic effect of chloroform inhalation. Necropsy showed features of alcoholic chronic pancreatitis.

Exposure of humans to chloroform was reported to result in increased serum biomarkers of AST, ALT, and LDH indicative of liver cell necrosis, symptoms of jaundice and hepatic coma, and liver degeneration and necrosis at autopsy (Rao et al., 1993). This case had increased AST, ALT, and LDH, jaundice and hepatic encephalopathy, and the leading cause of death were hemorrhages secondary to coagulopathy; autopsy revealed micro-vesicular steatosis. The finding of a fatty liver at post mortem examination is thought to also be a sign of death secondary to delayed chloroform poisoning (Schroeder, 1965; Choi et al., 2006). Abnormalities in the liver enzymes are observed to peak at 72–96 hours after a chloroform exposure and return to normal within 6–8 weeks (Meichsner et al., 1998; Choi et al., 2006). In the case reported here, liver enzymes increased over 20 times baseline in the first 24 hours and reached a peak on post-ingestion day 3.

Renal effects of chloroform were experimentally reported following oral and inhalation exposures, but evidence for chloroform-induced renal toxicity in humans is sparse (Wallace, 1950). In this case, pathology examination revealed typical renal lesions described in chloroform toxicity, such as tubular renal necrosis and glomerular hyalinosis and sclerosis.

The unconscious patient needs supportive treatment (under respiratory and cardiac monitoring) and possibly fluid replacement. Naloxone, dextrose and thiamine must be considered in obtunded patients (Hernandez, 2006). The patient presented here received 'coma cocktail' during transportation to hospital and supportive treatment in ED. Gastrointestinal decontamination is probably indicated after chloroform ingestion, also activated charcoal, and

whole bowel irrigation, which may decrease the absorption of chloroform (Choi et al., 2006). In this case, patient received activated charcoal in ED, mainly because an ingestion of a poison was suspected.

Table III.13. Complications in chloroform poisoning – literature review (reproduced from Lionte, 2010)

Author, year	Type of study	Route of exposure (dose)	Outcome	Complication
Kim H. 2008	Case report	Ingestion, attempting suicide	Recovery	Acute toxic hepatitis
Thouret et al. 1999	Case report	Ingestion	Recovery	Cardiogenic shock, liver failure
Thorpe et al. 1997	Review	Chloroform anaesthesia	Variable	Liver damage up to liver failure
Harada et al. 1997	Case report	Acute inhalation after chronic inhalation once or twice a month for 7 years	Death	Acute heart failure caused by arrhythmias or cardiac depression
Aiking et al. 1994	-	Exposure to higher inhaled air concentrations of chloroform in indoor chlorinated swimming pools	-	Renal toxicity (elevated β-2-microglobulin)
Rao et al. 1993	Case report	Injection (0.5 mL), and ingestion (half a cup), suicide	Recovery	Toxic hepatitis
Ger et al. 1993	Case report	Accidental inhalation	Recovery	Hepatic injury
Sarkar et al. 1990	Case report	Suicidal ingestion (30 mL of 30% solution)	Recovery	Respiratory insufficiency, heart arrest, hepatic injury
Hutchens et al. 1985	Case report	Intentional inhalation, recreational purposes	Recovery	Hepatotoxicity facilitated by long-term moderate alcohol consumption and arterial hypoxemia
Phoon et al. 1983	Occupational	Accidental exposure (80–160 mg/m^3 < 4 months)	Recovery	Toxic hepatitis
Linde et al. 1981	A historical mortality study	Anesthesiologists occupationally exposed to chloroform vapors (extent of exposure unknown)	Death	Possible association between cancer and chloroform exposure
Storms, 1973	Case report	Mistakenly ingestion, unknown quantity	Recovery	Cerebellar damage, toxic hepatitis.

Treatment of chloroform poisoning is symptomatic; no specific antidote is known or approved. However, N-acetyl-cysteine (NAC) has a role in the care of patients where glutathione depletion and free radical formation are thought responsible for toxicity, such as carbon tetrachloride and chloroform. NAC is being investigated as a treatment for agents associated with free radical and reactive metabolite toxicity, including chloroform, because it may minimize hepatic and renal toxicity by providing a scavenger for the toxic intermediate (Howland, 2006; Fung, 2007).

Rhabdomyolysis is commonly diagnosed in alcohol-intoxicated patients subjected to prolonged muscle compression (Huerta-Alardín et al., 2005). Our patient was a chronic alcoholic with a recent episode of binge drinking, which contributed to rhabdomyolysis appearance, together with muscle compression, and metabolic acidosis. The initial clinical sign of rhabdomyolysis in the case reported here was the appearance of discolored urine. Urine can range from pink-tinged, to cola-colored, to dark black. This patient presented tachycardia, weakness, and muscle and lumbar pain as general manifestations of rhabdomyolysis. The diagnosis of rhabdomyolysis was confirmed by laboratory studies (elevated serum CK of at least five times the normal value). CK rises in rhabdomyolysis within 12 hours of the onset of muscle injury, peaks in 1–3 days, and peak CK level may be predictive of the development of AKI (Ward, 1988). Abnormal CK levels are commonly seen in injured ICU patients, and a level ≥ 5000 U/L is related to AKI (Brown et al., 2004). This patient had a peaked CK of 10,409 U/L the third day after toxic exposure, predictive for AKI. Among complications of

rhabdomyolysis are hepatic dysfunction in 25% of patients (as a result of releasing proteases from injured muscles), and DIC (Huerta-Alardín et al., 2005). The early complications of rhabdomyolysis in our case were hyperkalemia, hypocalcemia, and elevated liver enzymes, and delayed complications were AKI and DIC. Continuous hemofiltration may be required initially to remove urea and potassium that are released from damaged muscles. Normalization of potassium is the priority (Ward, 1988). Even with potassium level normalized, despite using of hemofiltration, and other intensive care measures, the patient eventually died, because of coagulation abnormalities secondary to ALF.

The prospective study on blood glucose changes in acute poisoning with ethylic alcohol included 222 patients (20% of the total acute poisoning admitted to our department), which were divided in two groups of study. A control group was added, which included patients with ethanol addiction and ALD (table III.14).

Table III.14. Patients' characteristics and main results

Characteristic	**Group 1 (n=68)**	**Group 2 (n=154)**	**Group 3 (n=68)**
Gender, M/F	53/15	112/42	52/13
Age, years (mean ± SD)	39.36±15.52	39.05±16.34	42.5±10.13
Poisoning type (acute/chronic)	68/31	154/73	0/68
Clinical form (mild/moderate/severe)	12/15/41	59/84/11	16/19/33
Blood alcohol level (mg/dL)			
• 0.5-1.49	19 (28%)	42 (27.27%)	-
• 1.5-2.5	18 (26%)	62 (40.26%)	-
• >2.5	31(46%)	50 (32.47%)	-
Admission blood glucose (mg/dL):			
• normal (60- 110)	42 (62%)	74 (49%)	65 (96%) *
• hypoglycemia (< 50)	8 (12%)	41 (26%) *	0 (0%)
• hyperglycemia (>110)	18 (26%)	39 (25%)	4 (4%)
Type of OGTT curve (cumulative):			
• normal	22 (32%) *	-	3(4%)
• hypoglycemic	21 (30%) *	-	34(50%) *
• flat	10 (14%)	-	14 (20%)
• hyperglycemic (diabetes/IGT)	14 (20%)	-	19(26%)
• not interpretable	1 (4%)	-	-

M, male; F, female; SD, standard deviation; *, $p < 0.05$; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance.

The first group included patients admitted for acute ethanol poisoning and consisted of 78% males and 22% females. Among these, 46% were chronic alcoholics. Concerning the clinical form, 18% were mildly poisoned with ethanol (blood alcohol 0.5-1.49 mg/dl), 22% were moderate clinical forms (blood alcohol 1.5-2.5 mg/dl) and 60% were patients with alcoholic coma (blood alcohol level > 2.5 mg/dl). Only 32% patients had normal OGTT curves, hypoglycemia was recorded in 30% of the patients and hyperglycemic curves were present in 20% cases (Figure III.15).

The second group was represented by 154 subjects admitted to the ED for acute drunkenness, and these patients were evaluated only with blood glucose upon admission and blood alcohol level, along with liver function tests. 72.73% of these patients were males, and 47.4% of them were chronic drinkers. 38.31% were mild clinical forms of poisoning, 54.55% were moderate forms and 7.14% were severe forms. Admission blood glucose was normal in 74 patients (48.18%), hypoglycemia was recorded in 41 patients (26.31%) and 39 patients (25.45%) had hyperglycemia. Forty-one patients (26.31%) had abnormal liver tests.

The third group was represented by 68 patients with alcohol addiction and ALD. There were no significant differences with respect to the age of the patients between the groups

studied. The type of ALD was as follows: 16 patients had fatty liver, 19 patients had chronic alcoholic hepatitis and 33 patients had alcoholic liver cirrhosis stage Child A. The markers of chronic alcohol intake (increased GGT, macrocytosis) were present in all patients. This was also confirmed by the patients during history and after CAGE questionnaire. The types of OGTT curves recorded are presented in Figure III.15 (hypoglycemic curves and flat curves with delayed hypoglycemia were cumulated).

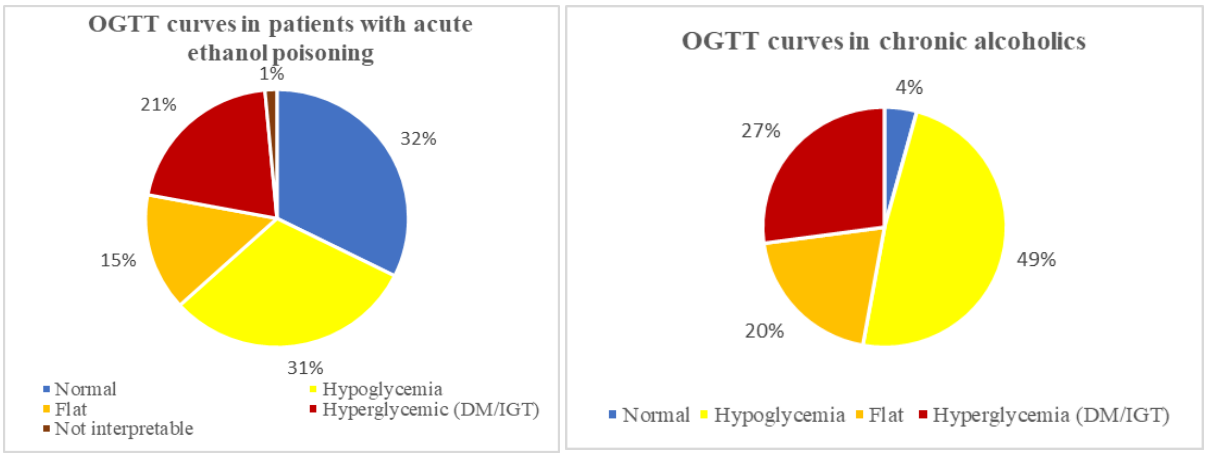


Figure III.15. Distribution of OGTT curves recorded in groups 1 and 3.

When analyzing the types of OGTT curves recorded, we noticed that flat curves with delayed hypoglycemia are significantly higher in group 3 (40%), as opposed with group 1 (8%, p 0.008). In patients with acute ethanol poisoning, normal OGTT curves were significantly more frequent, as opposed with group 3, where we recorded significantly more hypoglycemic curves. In patients with acute ethanol poisoning, who associated ALD, there were significantly more frequent hypoglycemic curves documented (11.9%, p 0.01), flat curves (8.33%, p 0.02), and diabetic curves (10%, p 0.01), as compared with normal curves recorded. In patients with alcohol blood level 0.5 – 2.5 mg/dL, the frequency of OGTT curves is not significantly different among groups. When blood alcohol level is > 2.5 mg/dL, we recorded significantly more IGT (50%), as opposed with normal curves (18.18%, p 0.02), diabetic curves (11.11%, p 0.02) and flat curves (15%, p 0.03). Alcohol addiction was frequently associated with hypoglycemic OGTT (40.62%) compared with normal curves (22.13%, p 0.04).

When we analyzed only admission blood glucose, for patients who couldn't be investigated with OGTT, we noticed that a normal admission blood glucose was recorded significantly more frequent in group 3 (96%), compared with group 2 (4%, p 0.006). Admission hypoglycemia (26.36%) was frequently noticed in group 2, patients admitted only in ED, compared with group 3 (0%, p 0.03).

Ethanol, and especially its metabolites (acetaldehyde and acetate) and excess of NADH and NADPH profoundly alter the carbohydrates, lipids, and proteins metabolic pathways. Ethanol itself has an anti-insulin effect through at least 2 mechanisms: a) direct aggression on beta-islet cells, followed by chronic calcified pancreatitis and pancreatic amyloidosis; b) increasing the catecholamines concentration, with a demonstrated hyperglycemic effect, as a consequence of adrenal gland hypersecretion, inhibition of synaptic reuptake of norepinephrine and catecholamines degradation (Dinca & Georgescu, 1999). Alcohol produces peripheral insulin resistance, as a result of abnormal glucose use, with direct effect on mitochondria volume and on muscle glycolytic enzymes. The NADH excess has hyperglycemic effect, because the glucose use is decreased (Krebs cycle is blocked) and the liver production of glucose is increased, as a consequence of intense glycogenolysis. Hypoglycemia can occur

when alcohol is ingested "à jeun", or in the situation of liver glycogen depletion, the gluconeogenesis being impaired (Grigorescu & Pascu, 1997; Dinca & Georgescu, 1999). This wide range of biochemical anomalies explains the various metabolic changes in ALD: hypoglycemia, IGT, and diabetes.

In patients acutely poisoned with ethanol, our results showed prolonged fluctuations of glucose level, with delayed hypoglycemia, 4-5 hours after glucose administration (both in patients with normal curves after 2 hours-OGTT, and in those with flat curves). These results are explained by the cellular humoral and hormonal alterations simultaneously produced in the setting of the poisoning. A special mention should be made regarding the flat curve with delayed hypoglycemia, seen in acute poisoning which affects the liver. Typically, hypoglycemia occurs 2 hours after glucose load. In these patients, glucose homeostasis, where the liver has a central role, fails to maintain a normal blood glucose, and a "delayed" hypoglycemia is recorded. The treatment of these patients should take into account this phenomenon, and a prolonged observation and monitoring and therapy are required to obtain and maintain the normal blood glucose level.

ALD, expressed as chronic alcoholic hepatitis, but mainly liver micronodular cirrhosis, presents with specific metabolic features, consequence of the effects of ethanol on both hepatocellular enzymes, the beta-islet cells from the pancreas, and implicitly, on insulin secretion. Hypoglycemia occurs either as a result of insulin excess, caused by a lack of degradation in a damaged liver, or the lack of glycogen deposits and an altered gluconeogenesis process unable to restore glucose homeostasis through the use of non-glucose substrates, the gluconeogenesis enzymes being also altered in case of chronic alcohol ingestion (Figure III.16).

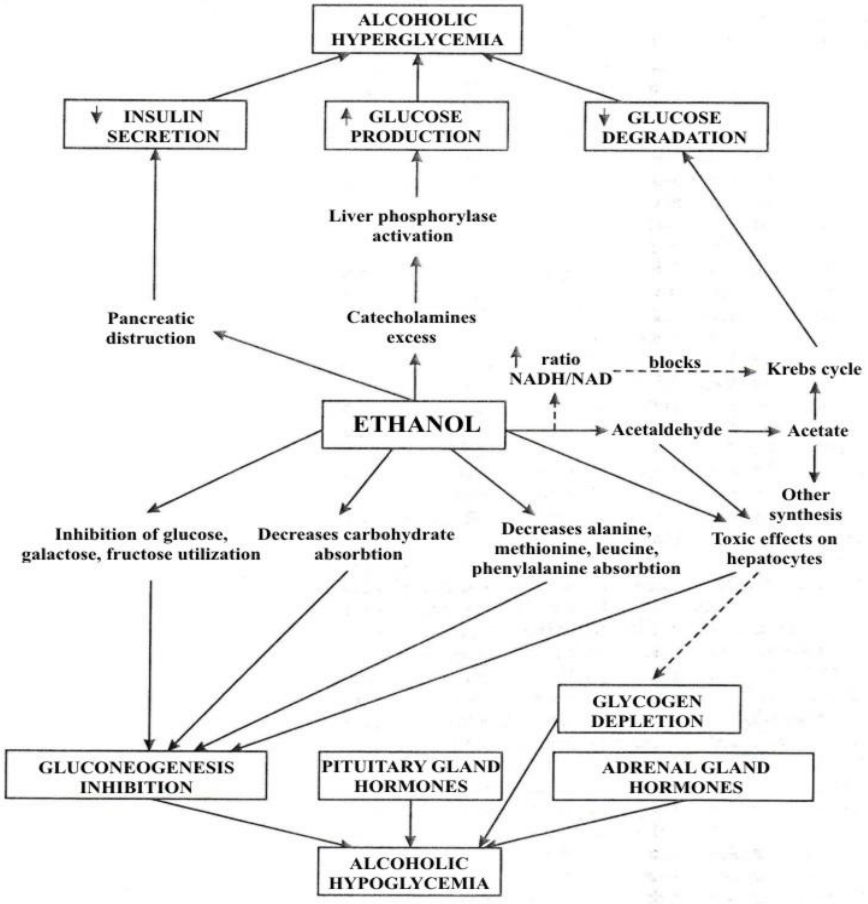


Figure III.16. The mechanisms involved in alcoholic hypo- and hyperglycemia (Lionte et al., 2005)

A randomized study on 100 patients from a rehabilitation center for alcohol addiction, who were evaluated with a 6 hours-OGTT upon admission, reveals that 60% of these patients had hypoglycemic curves, diabetic curves being recorded in 13% of cases, and the rest of 27% had flat curves (Mathews, 1997). Our results were consistent with this study in the sense that we recorded a small percentage of normal curves in 6-hours OGTT in chronic drinkers with ALD, and we also found delayed hypoglycemia, apart from "classical" 2 hours-OGTT. Hypoglycemia could have been missed if we would have stopped the test after 2 hours. The blood glucose should be monitored 5 to 6 hours after oral glucose load in OGTT, otherwise the impaired glucoregulation in patients with a history of ALD could escape an early diagnosis.

Conclusions

We reviewed the main features of chloroform acute poisoning and we made a literature review on the main complications associated with this toxicity. As a result, we emphasize the need for a thorough differential diagnosis of ALF, which should include ALD, acute poisonings (including chloroform), viral hepatitis, as well as other rare diseases (i.e., autoimmune hepatitis, Wilson's disease).

The prospective study used for the first time a prolonged 6-hours OGTT to investigate glucoregulation disturbances which occur in acute ethanol poisoning. We also characterized the glucose metabolic abnormalities in chronic alcoholics. We demonstrated that a delayed hypoglycemia occurs, 4-5 hours after glucose load, in acutely poisoned patients with ethanol, as well as in alcohol addicted patients, with associated ALD. This represents a delay in adapted physiological response, favored by the toxic liver disease. Acute and chronic ethanol poisoning is a risk factor for hypoglycemia, which mandates that observation and monitoring of glucose levels in these patients should be prolonged several hours after admission, mainly if a preexistent liver disease is present. To detect associated glucoregulation abnormalities, chronic drinkers with ALD should be subjected to a 6 hours-OGTT during hospitalization.

III.3. The effects of the food components on humans

This direction of research is reflected in the following published articles:
1. **Lionte, C.** An unusual cause of hypotension and abnormal electrocardiogram (ECG) - scombroid poisoning**.** *Cent Eur J Med* 2010; 5(3): 292-297 DOI: 10.2478/s11536-010-0003-z (ISSN 1895-1058) **(FI 0.244)**
2. **C. Lionte**, L. Şorodoc, O. Petriş, B. Varvara, V. Laba, L. Teodorescu, S. Teleman. Acute liver failure in poisoning with wild mushrooms. *Internal Medicine* 2004; I/New series (4): 53-58. (ISSN: 1220-5818)

Scombroid fish poisoning

Background

Scombroid or histamine food poisoning (scombrotoxism, scombroid ichthyotoxicosis) is a worldwide problem associated with significant morbidity. Scombroid poisoning is a clinical syndrome resulting from food consumption, especially Scombroidea fish (e.g., tuna, mackerel, albacore, bonito) or non-scombroid fish (mahi-mahi, amberjack) and cheeses that contain unusually high levels of histamine (Borade et al., 2007; Kow-Tong & Maison, 1987). Scombroid poisoning has been known for many years and was first reported in 1799 in Britain (Harrison & Bates, 2005). Although outbreaks of scombroid fish poisoning are frequently reported in Japan, Canada, United States, and other countries with a high dietary intake of fish, few cases are reported in Europe. The reason may be the resemblance of the symptoms with an

allergic reaction or other diseases, and its relatively short course, or the poor knowledge of medical personnel.

Aim of the research

We reported the first case series in Romania of severe scombroid poisoning presenting as marked hypotension and ECG changes, with complete recovery after intensive care. Given the low number of patients with this presentation, and the risk of cardiovascular complications, we considered useful to report this type of food poisoning to raise the awarness of the physicians in the ED. We reviewed the main features of scombroid poisoning and we discussed the therapeutical challenges faced in the ED in case of food poisoning.

Materials and methods

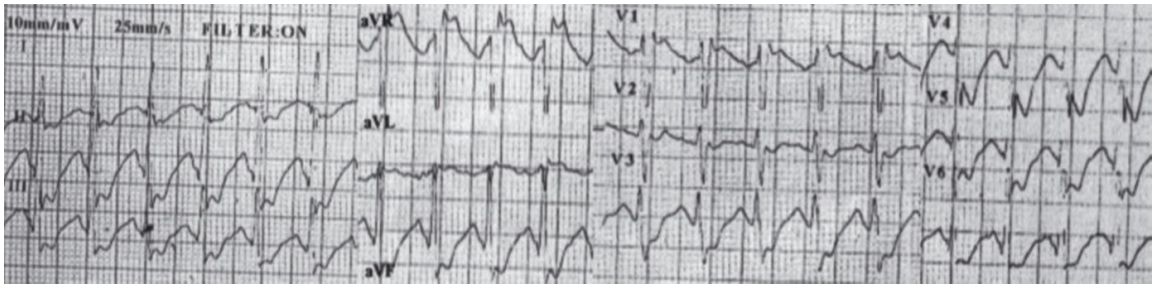
We retrospectively reviewed the charts of the patients admitted in 2009 for food poisoning, and we report a series of cases with severe cardiovascular manifestations after fish poisoning. The clinical picture, main ECG changes and laboratory tests were analyzed to be able to characterize this unusual poisoning.

Results and discussion

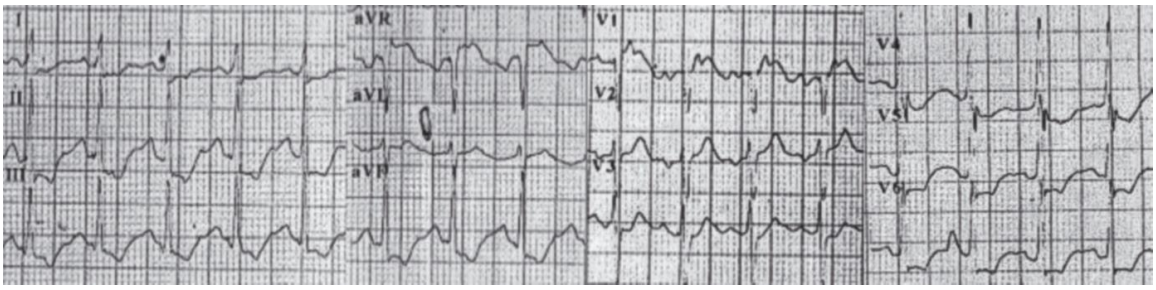
Three women aged 20, 26 and 44 were brought to the Emergency Department (ED) of an emergency regional hospital in North-East Romania, 30 minutes after eating fried mackerel. They declared that the fish had a peppery taste. Ten minutes after ingestion they all experienced flushing, headache, nausea, vomiting, anxiety and palpitations. Physical examination revealed diffuse macular blanching erythema all over the body surface, injected conjunctivae, tachycardia (140-150 beats/minute) in two cases, and heart rate 91 beats/ minute in the third case. Hypotension (BP 70-85/40-55 mmHg) was present in all cases. Cardiovascular examination revealed normal heart sounds, no murmurs or rub on auscultation. Neurological, respiratory and abdominal systems' examination was unremarkable. All patients' history was negative for cardiovascular, respiratory and allergic diseases. The ECG showed sinus tachycardia (150-138 bpm), widespread ST segment displacement (depression or elevation) with T wave changes in two patients (Figure III.17.A, Figure III.17.B), and accelerated idioventricular rhythm (AIVR) in the third case (Figure III.17.C).

Other significant laboratory changes were elevated blood glucose (ranged 6.93-8.52 mmol/l), and white blood cell count ranged 19.7-25.4x10^3/mmc. Repeated determination of cardiac enzymes, troponin T, electrolytes, renal function, and liver function showed normal values, during hospitalization. A clinical diagnosis of scombroid poisoning was established. The plasma histamine level was not measured in ED due to technical difficulties. All three patients underwent emergency resuscitation with intravenous fluids (crystalloid solutions 2000 ml in 1 hour followed by 80 ml/hour infusion for the next 6 hours) and subcutaneous epinephrine (0,5 mg sol. 1:1000, repeated after 15 minutes), intravenous diphenhydramine (50 mg, repeated after 4 hours) and cimetidine (300 mg, repeated after 6 hours), which determined a rapid improvement of clinical picture, BP, and ECG changes. They were all discharged from ED after 24 hours of observation, being asymptomatic and having normal ECG's.

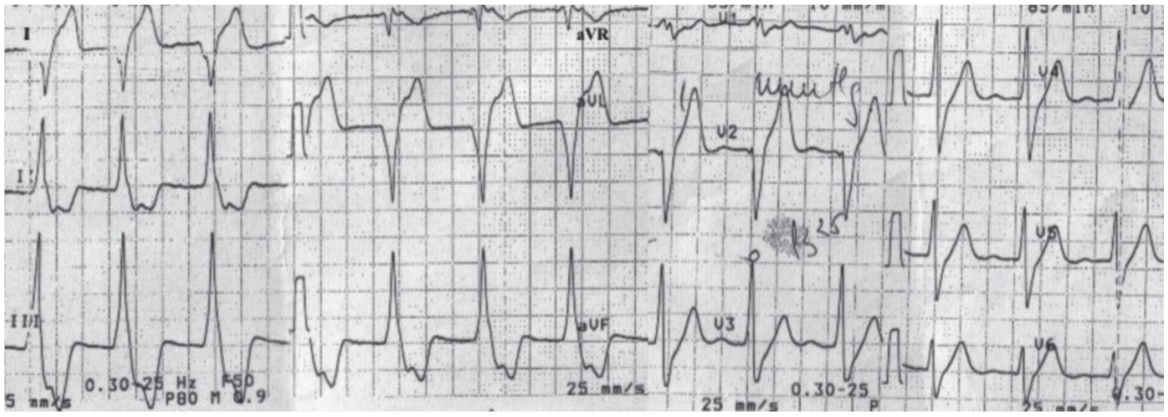
Scombroid fish poisoning accounted for 32% of reported illnesses associated with fish or shellfish consumption in United Kingdom and 50% in the United States of America in the 1990's (Lipp & Rose, 1997). It should be emphasized that scombroid poisoning is a toxic and not an allergic reaction, meaning that fish consumption does not have to be withheld. Cases reported here serve to highlight a rare, but serious presentation of scombroid poisoning.



A. Case 1: Sinus tachycardia 150 beats/minute with ST segment depression (2-5 mm) in anterior and inferior leads, and ST segment elevation 1-3 mm in leads aVR, aVL, V1.



B. Case 2: Sinus tachycardia 138 beats/minute with ST segment depression (2-4 mm) in antero-lateral and inferior leads, and ST segment elevation 1-3 mm in leads aVR, V1.



C. Case 3: Accelerated idioventricular rhythm 91-85 beats/minute with ST-T changes in inferior leads.

Figure III.17. ECG changes recorded in patients with scombroid fish poisoning

The time to onset of toxicity, the variety of clinical manifestations, and their distribution were in accordance with data in the literature (Table III.15). The illness typically runs a mild, self-limiting course with common clinical presentation of flushing, rash, pruritus, sweating, palpitations, headache, nausea, vomiting, abdominal pain and diarrhea (Harrison & Bates, 2005).

Table III.15. Classification and features of scombroid fish poisoning (Lionte, 2010)

Mild poisoning	Moderate poisoning	Major (severe) poisoning
Diffuse, macular, blanching erythema Flushing (face, neck, upper trunk) Sweating Burning of the mouth or peppery taste Tachycardia	Rash and persistent flushing Itching Headache Dizziness Tachycardia Gastrointestinal symptoms (nausea, diarrhea, abdominal cramps)	Localized swelling around the mouth and tongue Bronchospasm, wheezing and respiratory distress Hypotension or hypertension Acute pulmonary edema Disrrhythmias (atrial flutter, atrial tachycardia, transient AV block). Myocardial dysfunction, ischemia, or infarction.

The onset of symptoms usually occurs within a few minutes after the ingestion of the aforementioned food, but the effects of poisoning can last for up to a day. There are few isolated reports of adverse effects of scombroid poisoning such as hypotension, bronchospasm, anaphylactic shock, arrhythmias and visual loss (Harrison & Bates, 2005; Tursi et al., 2001). The pathogenesis of scombroid poisoning has not been clearly elucidated, however, it is generally associated with high histamine levels in bacterially contaminated fish, because histamine is heat stable and is not destroyed by different cooking methods (Lavon et al., 2008). Histamine toxicity is potentiated through inhibition of metabolizing enzymes that detoxify histamine, and the presence of putrescine and cadaverine (Al Bulushi et al., 2009). Histamine, putrescine and cadaverine are formed post-mortem in the muscular tissue of fish, through the action of certain microorganisms. Histamine interacts with several receptors and induces a variety of effects. A histamine concentration of 20 mg/100 g is considered to be the threshold to clinical poisoning, while levels over 100 mg/100 g are related to severe poisonings (Lavon et al., 2008; Harrison & Bates, 2005). The maximum level of histamine allowed by the Food and Drug Administration is 5 mg /100 g fish (Al Bulushi et al., 2009).

Histamine is an important chemical mediator of inflammation, vasodilation, increased vascular permeability, decreased peripheral resistance, airway smooth muscle contraction, gastric acid secretion, and induction of pain and itching through sensory nerve stimulation. Acting at H1- and H2-receptors, histamine induces the vascular endothelium to release nitric oxide, leading to vasodilation, erythema, increased vascular permeability, and edema (Simons, 2003). Vasodilation and reduced peripheral resistance may contribute to a significant fall in BP (Borade et al., 2007). Histamine can cause, directly or indirectly, coronary spasm, which is proposed as the main underlying mechanism of allergy-induced coronary syndromes (Gupta et al., 2001; Vigorito et al., 1987). Profound drop in contractility and dysrhythmias such as sinus tachycardia, atrio-ventricular blocks, ventricular tachycardia or idioventricular rhythm, during exposure to an allergen are directly proportional to the amount of released histamine. One could suppose that the amount of ingested histamine during scombroid poisoning is responsible for severe cardiac complications in some patients. In the course of anaphylactic reaction, ECG can reveal rhythm disturbances, as well as flattening or inversion of T waves and ST segment depression or elevation (Sinkiewicz et al., 2008). The ectopic and sinoatrial node automatism stimulation is H2 receptor dependent, whereas conductance disturbances are H1 receptor mediated (Levi et al., 1978). Patients presented here developed severe hypotension, which could contribute, along with histamine effects, to ECG abnormalities. Scombroid poisoning is often misdiagnosed and as a result, underreported. Diagnosis can be easily confused with allergic reaction, mainly when only one patient presents. History of recent fish consumption, especially mackerel or tuna, should raise the suspicion of such poisoning. Symptoms related to histamine poisoning can also be similar to those of coronary heart disease, increasing the possibility of an invasive medical intervention if misdiagnosed (Becker et al, 2001).

Mild scombroid poisoning (Table III.15) must be differentiated of anaphylaxis, bee and Hymenoptera stings, erysipelas, poisoning due to other types of fish (Ciguatera, Shellfish, puffer fish) and monosodium glutamate reaction. Symptoms of moderate poisoning could resemble migraine or cluster headache, niacin-like reaction, disulfiram reaction and Zollinger-Ellison syndrome. Features of severe scombroid poisoning could lead to confusion with angioedema, anaphylactic shock, carcinoid syndrome, pheochromocytoma, mastocytosis, toxic shock syndrome, or acute coronary syndromes (Predy et al., 2003; Chegini & Metcalfe, 2005; Sobel & Painter, 2005). Diagnosis of scombroid fish poisoning is clinical, based on thoroughly ascertaining the patient's medical history and having a high index of suspicion. In the cases reported here, the diagnosis was clinical, because the typical symptoms appeared shortly after ingestion of scombroid fish (mackerel). Although not performed routinely, blood sampling

within 4 hours of ingestion of contaminated fish may yield a high plasma histamine level, and analysis of fish flesh may confirm the presence of toxin (Bédry et al., 2000). Extremely rare reported cases of myocardial dysfunction, ischemia, or infarction related to scombroid poisoning exist (Grinda et al., 2004; Ascione et al., 1997). The patients presented here had serious ECG changes: sinus tachycardia, ST segment depression (2-5 mm) in anterior and inferior leads with ST segment elevation in leads aVR, V1 (case 1 and 2), and AIVR 85 beats/min, with 5-7 mm ST segment depression in inferior leads (case 3). These changes are the expression of myocardial ischemia (secondary to coronary spasm induced by histamine, and to severe systemic hypotension which could impair coronary perfusion), as well as the effect of histamine on H2 receptors that can stimulate sinoatrial node automatism. AIVR is a form of ectopic or automatic ventricular arrhythmia, produced by enhanced automaticity of the myocardial cell, which can occur under certain abnormal metabolic conditions, including myocardial ischemia (especially inferior wall ischemia or infarction), digoxin toxicity, hypokalemia, and hypoxemia (Singh & Sharma, 2009). In case 3, there were ECG signs of inferior wall ischemia, which could explain the episode of AIVR. Symptoms of scombroid poisoning usually subside in 8-12 h. The use of emesis is not indicated, as symptoms occur rapidly, vomiting being a primary effect of the toxin (Harrison & Bates, 2005). Despite the paucity of data from clinical trials, H1-antihistamines are effective in ameliorating the symptoms of scombroid poisoning. H2-antihistamines may also shorten the course of illness (Lavon & Lurie, 2008). Supportive measures include adequate rehydration and appropriate antiemetic therapy. For most mild cases, prompt antihistamine treatment is effective and sufficient (Sobel & Painter, 2005). Corticosteroids are not needed, except in the case of bronchospasm since the illness is a toxic reaction and not an immune or allergic one (Harrison & Bates, 2005). Major scombroid poisoning can induce severe hypotension requiring intravenous fluids and inotropic support with dopamine infusion and intravenous (IV) epinephrine (Tursi et al., 2001). Patients presented here responded well to intravenous fluids, subcutaneous epinephrine and antihistamine therapy, without the need of IV epinephrine. We have to consider the risk of IV epinephrine itself, which was associated with acute myocardial infarction immediately after IV administration for anaphylactic reaction, presumably as a result of epinephrine-induced coronary vasospasm (Shaver et al., 2006). Scombroid poisoning can be prevented by keeping the dark-fleshed fish refrigerated below -15 ºC and by avoiding of consuming fish that had been kept in opened cans for several days (Lavon & Lurie, 2008).

Limitations of the study: This analysis has the limitations of an observational retrospective study. We included a relatively small sample size of selected poisoned patients from a single-center unit.

Conclusion

The case series presented represents the first report on patients with scombroid fish poisoning in Romania. They presented a severe form of scombroid poisoning, with diffuse erythema, hypotension, palpitations and ECG changes, after fried mackerel ingestion. The medical personnel is not familiar with this food born disease, and such cases could be easily misidentified as anaphylactic shock, or ischemic coronary event, and could lead to inappropriate medical intervention. When facing a patient with cardiovascular compromise in ED, one should include fish poisoning in the differential diagnosis.

Wild mushroom poisoning

Background

Although morbidity and mortality after wild mushroom poisoning are a health problem especially in Europe, where traditional cuisine uses a wide range of mushroom dishes, the United States and Australia report the same problem, especially cases recorded in immigrants from Europe (Bryngil, 1999). These mushrooms are widely found in coniferous and broadleaf forests, in rainy season or autumn. The mushrooms species recognized to have hepatotoxicity, up to fulminant liver failure, are those with a long latency of clinical symptoms onset, such as Amanita Phalloides and Galerina marginata. The toxins contained in these mushrooms are not destroyed in cooking, refrigeration or drying process. Amatoxins enter the hepatocytes and lead to acute severe toxic hepatitis, which may evolve to fulminant liver failure. The lethal dose for amatoxin is estimated to be 0.1-0.3 mg/kg, quantity which is present in only one mushroom (Bryngil, 1999, Klein et al, 1989)

Acute or fulminant liver failure (FLF) is a syndrome characterized by association of hepatic encephalopathy with signs of hepatic insufficiency (jaundice and coagulopathy) and frequent signs of multi-organ failure, which occur in a patient with an acute liver condition, without a history of hepatic diseases (Grigorescu & Pascu, 1997). The definition usually involves an interval of 8 weeks from jaundice onset. However, a distinction should be made between FLF, which occurs after 2 weeks and sub-fulminant liver failure, which takes 2 to 8 weeks from jaundice onset to develop. The distinction is important in terms of evolution. The decision for a liver transplantation should be more rapid in a patient with FLF, compared with one with a sub-fulminant liver failure (Sherlock & Dooley, 1993).

Aim of the research

We aimed to analyze ALF which can complicate the evolution of acute wild mushroom poisoning, to detect the risk factors for liver toxicity and to emphasize the practical consequences for the diagnosis, outcome and therapy in these patients.

Materials and methods

A prospective study on wild mushroom poisoning included, from January 2001 to December 2002, 61 patients admitted in Internal Medicine Clinic and ICU of the Emergency Clinic Hospital Iasi. We recorded clinical signs and symptoms of ALF associated with symptoms of acute mushroom poisoning. All patients had paraclinical tests determined upon admission and follow-up. Mushroom poisoning had a prevalence of 12% among all cases admitted with an acute poisoning during the period analyzed (1034 patients). Statistical methods were t Student's test, to analyze the significant differences for continuous variables, and Chi square, to test the hypothesis or to analyze categorial variables.

Results and discussion

Sixty-one patients were admitted for wild mushroom poisoning, 27 men and 34 women, with 55.74% patients with residence in a rural region. Patients with mushroom poisoning were predominantly of young age (Figure III.18).

The latency period before the symptoms' onset was < 6 hour in 44 patients (72.13%), the rest of cases having a longer period before the onset of the disease. Associated comorbidities were: respiratory diseases (1.64%), liver diseases (9.84%), cardiovascular diseases (18.03%) and alcohol addiction (19.67%).

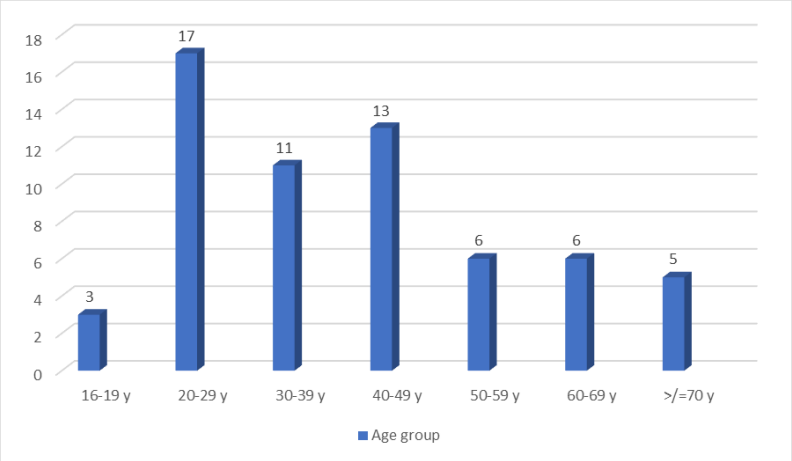
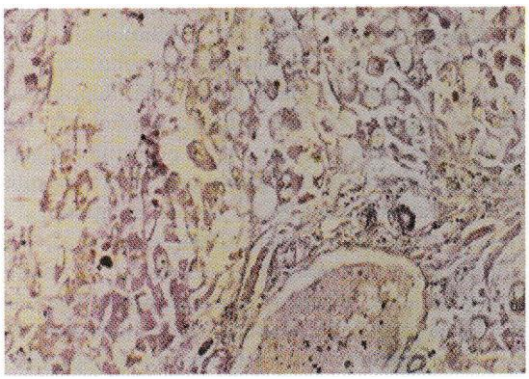


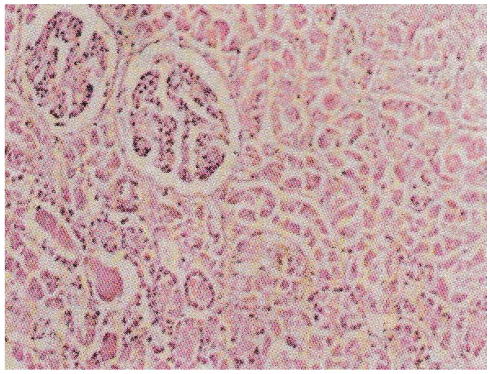
Figure III.18. Age distribution in patients admitted with mushroom poisoning

The clinical syndrome of mushroom poisoning was: gastrointestinal irritant (54.1%), muscarinic (16.39%), gyromitrin poisoning (16.39%), amatoxin poisoning (11.48%), and Paxillus syndrome (1.64%). All patients with a delayed onset of clinical signs and symptoms associated in evolution liver and kidney complications. Hepatic cytolysis was recorded in 36.07% case and cholestasis in 24,59% cases. The patients with an early onset of clinical symptoms (under 6 hours) had a simple evolution, without complications. Hepatic cytolysis was frequently associated with amatoxin poisoning (100%) as compared with muscarine poisoning (10%, p 0.001) and gastrointestinal irritant syndrome (12.12%, $p < 0.001$). Also, in gyromitrin poisoning, hepatic cytolysis was detected significantly more (90%) than in muscarine poisoning (10%, p 0.001) and gastrointestinal irritant syndrome (12.12%, $p < 0.001$). Hepatic cholestasis was significantly associated with amatoxin poisoning (100%) compared with gyromitrin poisoning (50%, p 0.02), and gastrointestinal irritant syndrome (6.06%, $p < 0.001$), while it was absent in muscarine poisoning. These data are in accordance with literature reports, which mention the association of toxic hepatitis in both amatoxin and gyromitrin poisoning (Klein et al., 1989). Five patients (8.2%) associated hypoglycemia, in the setting of ALF induced by amatoxin poisoning. The poisoning was confirmed by typical clinical signs and symptoms (onset 10 hours after mushrooms' ingestion in all patients who consumed the dish, associated liver and renal failure), and by pathology examination, in deceased patients, with detection of the spores of Amanita phalloides and typical lesions in the liver and kidney (Figure III.19).

Transaminases and bilirubin were normal the first 24 hours after mushrooms' ingestion, and began to increase after 48 hours, with a peak in the fourth-fifth day after ingestion, followed by a slow decrease to normal values, in survivors. In deceased patients, although transaminases had a tendency towards normalization, the continuous increase in cholestasis failed to respond to therapy which finally led to death. We noticed only a moderate increase in BUN and creatinine, as opposed with tubular necrosis lesions reported in pathology examination in 3 patients with amatoxin poisoning who deceased. One of the patients, who was admitted 3 days after mushrooms' ingestion had elevations in BUN and creatinine upon admission and developed anuric AKI, which failed to respond to therapy, and died. Hypoglycemia was recorded when the liver was severely damaged, hours before death. We interpreted that as a sign of collapse of liver function, knowing the central role it plays in glucose metabolism. The majority of the patients had a favorable evolution, only 6 deaths being recorded (9.84%) in patients who ended with FLF, hypoglycemia being documented before the end.



Fragment of portal-biliary space showing massive necrosis of hepatocytes, biliary thrombi. Hematoxylin-eosin stain x 20.



Fragment of kidney showing normal glomeruli, tubular necrosis, images of tubular regeneration. Hematoxylin-eosin stain x 40.

Figure III.19. Specific pathology lesions in amatoxin poisoning

Hypoglycemia is documented in 40% adult patients with fulminant liver failure. It is considered to be a sign of acute liver insufficiency, and it is explained by increased levels of circulating insulin, the reduced gluconeogenesis and glycogen liver deposits, secondary to hepatocytes' necrosis and impaired glycogenolysis. The clinical manifestations are masked by hepatic encephalopathy, and for detecting it, hourly determination of blood glucose is recommended (Grigorescu & Pascu, 1997).

Acute poisoning with Amanita phalloides manifests as an amatoxin poisoning. Other mushrooms which contain amatoxins could be involved, such as Amanita verna, A. virosa and mushrooms from Galerina and Lepiota species (Klein et al., 1989). Two types of toxins are involved in the pathogenesis of this poisoning: the amatoxins and the phallotoxins, which are responsible for gut, liver and renal tubular necrosis, potentially fatal (Bryngill, 1999; Lionte et al., 2002). Amatoxin poisoning in humans evolves in four clinical phases: latency, which lasts 6-12 hour after mushroom ingestion, aggression phase, characterized by sudden onset of gastroenteritis, a third phase, when the symptoms are declining, and a final phase, when the features of liver and renal failure appear together with myocardial dysfunction. Between the fourth and the eighth day after onset, hepatic coma ensues, with associated acute kidney failure, which contributes to death (mortality rate 40-90%). The diagnosis is suspected by the clinical features (delayed onset, more than 6 hours after mushroom ingestion, with characteristic evolution in four phases) and confirmed by laboratory tests which demonstrate the severity of liver insufficiency and toxicological exams: detection of amatoxins using radioimmune assays, high performance liquid chromatography, mycologic examination of the mushroom specimen and microscopic identification of spores in gastric content, stools, or pathology specimens(Bryngill 1999; Ellenhorn, 1997). We noticed that transaminases and bilirubin were normal in the first 24 hours after ingestion, and began to increase after 48 hours, with a peak in the fourth-fifth day after admission, followed by a slow decrease in transaminases values, but continuous increase of bilirubin, followed by death. Two patients, who were admitted late after mushrooms' ingestion (2-4 days), had from the beginning very high values of the above parameters and high creatinine levels. We also noticed a moderate increase in creatinine levels, contrasting with the severity of tubular necrosis found in pathology exam in patients who didn't survive.

In our study, the evolution and outcomes were unfavorable in patients admitted late, after 2-5 days of evolution without medical therapy, in those who were older and in those who ingested large amounts of mushrooms. All patients received intensive care therapy for liver failure and sessions of hepatic dialysis (Molecular Adsorbent Recirculating System), with a

good outcome only in one patient. There were no technical possibilities for a liver transplantation. Until the present study, no liver assist device proved to be useful to improve the outcomes in amatoxin poisoning. Several modalities for temporary liver support were tested, from hemoperfusion and hemodialysis, hepatic dialysis, to the most invasive, such as hepatocyte transplantation, auxiliar heterotopic liver transplant and finally orthotopic liver transplant. Hemoperfusion and hemodialysis had a modest beneficial effect in the decrease of GCS score, while extracorporeal liver assist devices using cartridges containing living hepatocytes from other species of from tissue cultures appeared to be promising for sustaining liver function to recovery, or to liver transplantation (Lionte et al., 2002). In non-survivors, death was recorded eight to ten days after mushroom ingestion, preceded by the complications of the liver failure (hepatic coma, coagulopathy, bleeding and cardiovascular collapse) and renal failure.

Limitations of the study: This analysis has the limitations of an observational retrospective study with many variables which were analyzed.

Conclusion

Wild mushrooms poisoning has a maximal incidence between July and November. The macroscopic appearance is deceiving, so confusion with edible species is frequent, even for persons who are familiar with the mushroom species. Severe clinical picture has a variable latency, which might explain delayed presentation to the hospital, when decontamination measures and toxin elimination are no longer possible, and the lesions in target organs are already present. The hospitalization is mandatory in every patient with a mushroom poisoning, when the onset of symptoms is delayed more than six hours, despite the normal liver and renal function tests in the first 24 hours, and even for fragile patients (children, elders) with an early onset (below six hours). The liver and kidney acute failure as a result of amatoxin poisoning have a poor prognosis. Hypoglycemia in wild mushroom poisoning occurs when liver is failing, being a poor outcome indicator in this poisoning.

III.4. Epidemiological studies on acute poisoning in Iasi County.

This direction of research is reflected in the following published articles:

1. Sorodoc, V; Jaba, IM; **Lionte, C;** Mungiu, OC; Sorodoc, L. Epidemiology of acute drug poisoning in a tertiary center from Iasi County, Romania. *Hum & Exp Toxicol.* 2011; 30(12): 1896-1903. (ISSN: 0960-3271) **(FI 1.772)**
2. Gazzi, EN, Sorodoc, V, Jaba, IM, **Lionte, C,** Bologa, C, Lupusoru, CE, Lupusoru, R, Sorodoc, L, Petris, O. Profile of adult acute cholinesterase inhibitors substances poisoning - a 30 years analysis. *Open Medicine (formerly Central European Journal of Medicine)* 2015; 10(1): 278-284. (ISSN 2391-5463). **(FI 0.209)**
3. **C. Lionte**, L. Şorodoc, V. Şorodoc, O. R. Petriş. Acute isoniazid poisoning: epidemiological features, diagnostic challenges and management – overview on cases recorded over 10-years period in an urban hospital. *Timisoara Medical Journal* 2006; 56(suppl.2): 183-188. ISSN 1583-5251

Background

Acute poisonings are common situations in the emergency departments all around the world and involve high medical attention and significant costs. Poisoning with pharmaceutical products is ubiquitous, as we can see in the reports originating from very different countries (Bronstein et al., 2008; Repetto, 1997; Ahmadi et al., 2010; Camidge et al., 2003; Fernando, 2002) In 2008, acute drug poisonings were found to be the first cause of acute poisoning in

USA. In the top 25 substance categories associated with the largest number of fatalities, the first five positions were occupied by drugs poisonings (Bronstein et al., 2008). In the US, a surveillance of cases of isoniazid (isonicotinic acid hydrazide - INH) poisoning by the American Association of Poison Control Centers' National Data Collection System from 1985 to 1993 revealed a low number of 138 cases in 1985, with no fatalities, and a high number of 2656 cases in 1991, with 6 fatalities (Mechem).

Acute cholinesterase inhibitor substances (CIS) poisoning is a major health problem accounting for significant morbidity and mortality worldwide (Kishi & Ladou, 2001). The etiological profile of cholinesterase inhibitors poisoning varies in different world regions. In developing countries, where there is a lack of regulation and surveillance, inadequate protective equipment, and a large sector of agricultural industry, the incidences are expected to be higher. In some countries, such as China and Sri Lanka, self-poisoning with pesticides is a particularly severe problem (Zhang et al., 2013; Eddleston et al., 2006). The main circumstances of poisoning are suicide, homicide, accidental and occupational exposure. Since occupational and accidental poisoning require a specific prevention and control measures, and suicidal exposures need a specific attention and predisposing factors assessment, it is important to accurately determine the magnitude of the problem through better estimates of cases and deaths resulting from cholinesterase inhibitors toxicity.

There are many differences with respect to the pattern and cause of acute poisoning between geographical regions, even within the same country, and there is a constant need for new information in this field, in order to develop educational and prevention programs (Islambulchilar et al., 2009).

Few epidemiological studies exist in Romania, concerning acute poisoning and to our knowledge no study on acute drug poisoning epidemiology in this region has been previously published in an international medical journal. Although extensive data is available regarding the pattern of pesticide poisoning in many areas of the world, the data regarding the epidemiology of poisoning in an EU region (Northeastern part of Romania) is very scarce.
These studies were aimed to provide a detailed screening on aspects of the pattern and outcome of drugs, with a focus on IHN, and acute cholinesterase inhibitors poisoning cases in North-Eastern Romania, to compare our experience with the data reported by the researchers from other countries, to identify the risk factors for drug and cholinesterase inhibitors poisoning, in order to stimulate better preventive and management strategies.

Materials and methods

First, we performed a retrospective study over a ten-years period on 12.166 records of patients admitted with acute poisoning in Emergency Clinic Hospital Iasi, of which we extracted 174 files of patients poisoned with IHN, all in suicide attempt.

Several years later, we retrospectively reviewed the medical charts of all patients with acute drug poisoning who were admitted in our department between January 2003 and December 2009. The selection of cases was based on the patient's diagnosis on discharge and was accomplished through analysis of all the medical records of the patients hospitalized in our Internal Medicine and Toxicology Department, for the last 7 years. A number of five physicians participating in the study abstracted the charts using a standardized data collection form, in a Microsoft Excel spreadsheet. This collection form was designed for this purpose and included the following variables: demographical characteristics including age, gender, occupation, residence (rural or urban area) and type of exposure (intentional or accidental); drug category; clinical form of poisoning (mild, medium, coma); number of pills; provenience of the drug (prescribed by the family physician, family members and pharmacy); the time between the poisoning and the admission to the hospital; previous history of poisoning; history of

psychiatric disease; blood alcohol levels; length of hospital stay and clinical outcome. When the information was not available, it was classified as unknown.

The abstractors were trained in data abstraction by the principal investigator. Inter-rater reliability was calculated by using 42 (6 per year) medical charts. All five abstractors reviewed the entire set of randomly selected medical charts. Inter-rater agreement was assessed by using k analysis (Gilbert et al., 1996). The inter-rater reliability was assessed after the finalization of the medical records abstraction.

The drugs were classified as benzodiazepines, barbiturates, neuroleptics, anticonvulsants, antidepressants, cardiovascular drugs, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) and nonopioid analgesics, antibiotics, glucose lowering drugs, opioids, tuberculostatic agents, other medications (vitamins, antithyroid drugs, iron compounds, etc.) and unknown.

The third study retrospectively reviewed all the acute CIS poisonings cases admitted to our hospital from January 1983 to December 2013. The information was obtained from medical hospital records. The selection of cases was based on the patient's diagnosis at discharge and decreased level of plasma butyrylcholinesterase (normal value 5-11 u/ml) through analyzing all the medical records of the patients hospitalized in our Internal Medicine and Toxicology Department. Physicians participating in the study abstracted all the data from the medical records. Data include patient's demographics (age, gender, occupation, residence), type and routes of exposure, clinical presentation, clinical forms of poisoning (mild, moderate, severe) according to W.H.O. classification of severity, history of psychiatric disease, associated alcohol intake, factors responsible for poisoning, plasma cholinesterase on admission, gastric lavage, the time between the exposure and hospital presentation, as well as clinical outcome.

Patients who did not require admission to the toxicology department and were discharged from the emergency unit were not included in these studies. The adverse reactions, the drugs secondary effects and chronic poisonings were also excluded.

The databases thus created were analyzed using SPSS for Windows 18.0. In the statistical analysis, the chi-square test for comparing nominal variables was used when proportions were analyzed for significant differences. For numeric variables, means were compared using ANOVA one-way analysis of variance, followed by Bonferroni post hoc test. Differences are considered statistically significant when p values are under 0.05 (Jaba et al., 2010).

The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Results of the first epidemiological study

IHN poisoning incidence ranged 0.2 to 4.09% of all acute poisonings, the lowest incidence being recorded in 2002 (Figure III.20).

IHN poisoning appeared to be more frequent in young, unemployed women (Figure III.21), aged 16 to 35 years (64.36%), with previous history of psychiatric illness (31%) or tuberculosis (TB) – 27%. Also, 61% of cases had a family history of TB. The total amount ingested ranged from 4.3 to 25 g (mean, 14.65 g). IHN toxicity induced, within 30 minutes to two hours after ingestion, nausea, vomiting (46%), slurred speech, dizziness (54.2%) and tachycardia (76.3%), followed by stupor, coma (39.4%) and grand mal seizures (100%).

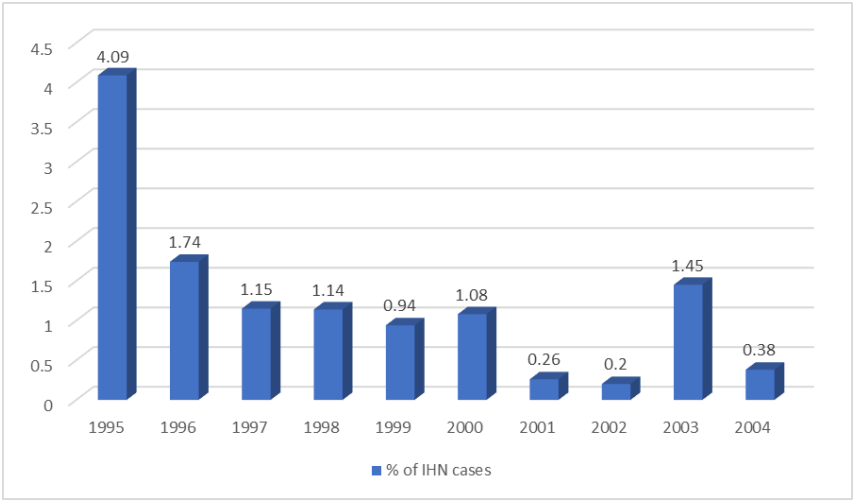


Figure III.20. Incidence of acute IHN poisoning over a 10-years period

Diagnostic challenges were encountered mainly in the situation of comatose patients with no history data, seizures and acidosis.

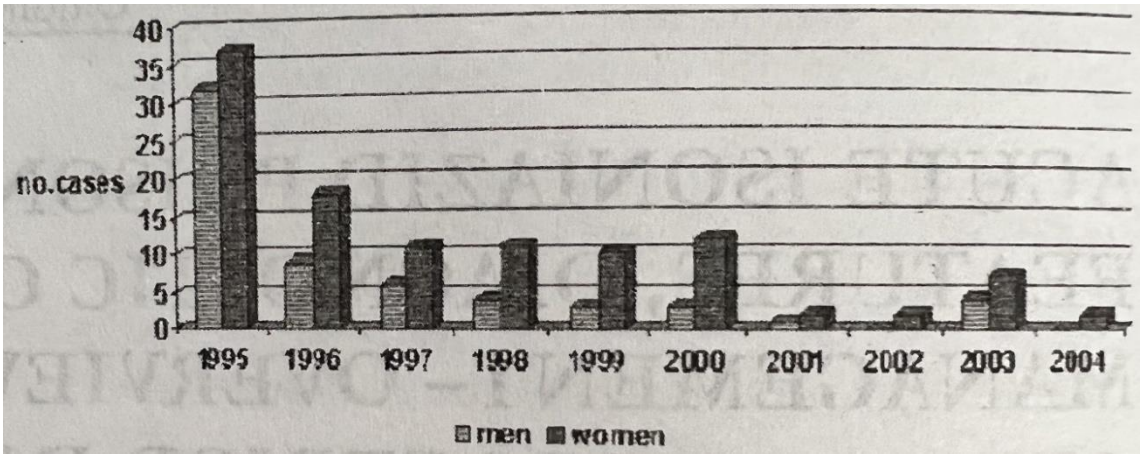


Figure III.21. Distribution of acute poisoning with IHN based on the gender

Laboratory studies showed leukocytosis (81.4%), an elevated anion gap and metabolic acidosis (57.2%), hyperglycemia (39.9%), hypokalemia (38.7%), impaired liver tests (20.7%; peak aspartate aminotransferase 1,280U/L), glycosuria and ketonuria (14.6%). Rhabdomyolysis (59.8%, peak creatine kinase 18,000 U/L), and neurotoxicity (including peripheral neuropathy - 8 cases, toxic encephalopathy - 3 cases, cerebellar syndrome - one case, transient memory impairment - 6 cases, delirium - 4 cases) were the most frequent complications recorded. Creatine kinase was elevated at an ingested dose of more than 2.7 grams, and values peaked on days 5 or 6 after admission. Statistically significant correlations were observed for the elevation of creatine kinase with the amount of drug ingested and the frequency of seizures. No correlation was observed between elevated creatine kinase and the delay in presentation to hospital. Five patients with refractory seizures died (2.95%), after failure to respond to anticonvulsants and parenteral pyridoxine, all of them being with a blood alcohol level of 200 mg/dl. Intravenous pyridoxine, as well as supportive therapy and drug decontamination were used in all cases.

Results of the second epidemiological study

Between 2003 and 2009, a number of 2852 cases of acute poisonings were recorded in our clinic, and among those, drug poisonings represented 28.43% (811 cases). The highest numbers of drug poisoning cases were hospitalized in 2005, up to a total of 170 cases (Figure III.22).

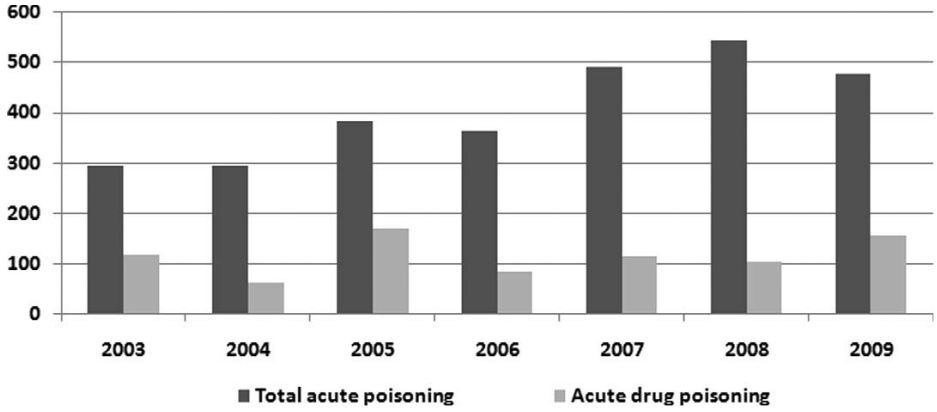


Figure III.22. Incidence of acute poisoning between 2003 and 2009.

The majority of the poisonings were voluntary (97.27%), for suicidal purposes. More than half of the patients (65.88%) used only one drug, while in 32.92% of the poisonings the patients took a form of poly-medication (Figure III.23). The poisonings were a mixture of drugs with non-medicinal substances in only a few of the recorded cases (10 patients): seven cases that associated small amounts of corrosive substances, one cannabis and two pesticide compounds.

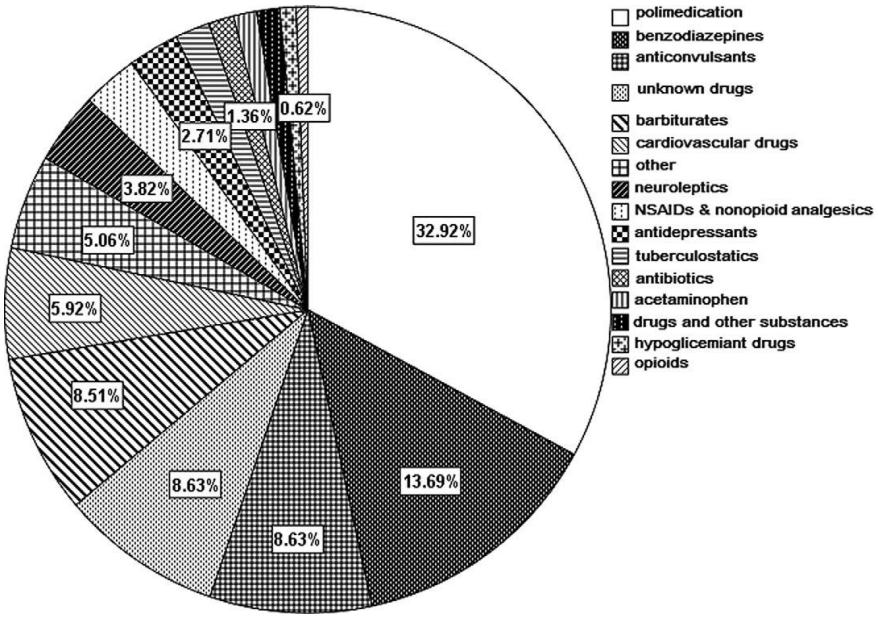


Figure III.23. Categories of drugs involved in acute drug poisonings between 2003 and 2009.

The most frequently involved drugs were the benzodiazepines (13.69%), followed by anticonvulsants (8.63%), barbiturates (8.51%) and cardiovascular medication (5.92%). From the total number of drug poisonings, the highest incidence was recorded in women 66.46%

(Table III.16), 39.94% patients were unemployed, 35.78% had undergraduate education and 19.11% were retirees.

The lowest incidence of drug poisonings was observed in the group with graduate education (5.17%). The majority (61.67%) of the patients came from urban areas. The 21–30 years age group had the biggest incidence, 29.8%, while patients over 70 years old, 3%, were less frequently hospitalized for drug poisonings (24 cases; Table III.17).

The number of pills ingested varied highly, with an average of 33.87 + 33.63, frequently from personal medication prescribed by the personal physician (41.15%), from family (37.69%) or bought directly from the pharmacy (21.16%).

Most of the cases had mild (51.94%) or medium clinical manifestations (28.35%). Coma was recorded in only 19.71% of the cases. More women manifested severe clinical forms than men (p 0.013). Also, higher frequency of severe clinical forms was observed in patients without history of psychiatric diseases (p 0.006) and blood alcohol levels over 150 mg/dl ($p < 0.001$). A previous psychiatric report was present in 13.81% of the cases. For a total of 77.8% of patients, this was the first attempt, 11.7% patients had history of two suicide attempts and 10.5% had records for more than two. A higher rate of repeated attempts was accompanied by cases with two or more medicines involved (p 0.035), and repeated attempts were more frequent for 31–40 age group (p 0.023), urban areas (p 0.001), patients with psychiatric history ($p < 0.001$) and unemployed patients (p 0.037), using their own medication for the suicidal attempt (p 0.042).

Table III.16. Distribution of acute drug poisoning in gender groups

Category	Cases No.	Gender (%) Men	Women
Polymedication	267	32.6	67.4[a]
Benzodiazepines	111	41.4	58.6[a]
Anticonvulsants	70	45.7	54.3[a]
Barbiturates	69	23.2	76.8[a]
Cardiovascular drugs	48	29.2	70.8[a]
Other	41	29.3	70.7[a]
Neuroleptics	31	22.6	77.4[a]
NSAIDs and nonopioid analgesics	24	37.5	62.5[a]
Antidepressants	22	22.4	77.3[a]
Tuberculostatics	15	40	60[a]
Antibiotics	11	9.1	90.9[a]
Acetaminophen	10	20	80[a]
Drugs and other substances	10	60	40
Hypoglycemiant drugs	7	28.6	71.4[a]
Opioids	5	20	80[a]
Unknown drugs	70	37.1	62.9[a]
Total	811		

NSAIDs: nonsteroidal anti-inflammatory drugs; [a], the difference is significant at the 0.05 level.

The lowest frequency of repeated suicide attempts was recorded for the groups with graduate education or over 60 years old, while for patients over 70 only one previous suicidal attempt was recorded.

Alcohol intake was more frequent in men (27.2% had levels over 50 mg/dl) than in women (17.4% had levels over 50 mg/dl). Higher levels of blood alcohol were registered in

men: 17.1% of men compared with 11.2% of women had blood alcohol levels over 150 mg/dl (p 0.014).

Table III.17. Distribution of acute drug poisoning in age groups

	Age							
Category	18–20	21–30	31–40	41–50	51–60	61–70	>70	Cases No.
Polymedication	49	81	63	23	31	14	6	267
Benzodiazepines	12	34	26	18	12	4	5	111
Anticonvulsants	8	22	25	10	5	–	–	70
Barbiturates	9	20	19	14	3	2	2	69
Cardiovascular drugs	6	14	10	5	8	2	3	48
Others	11	12	6	3	4	1	4	41
Neuroleptics	6	8	7	5	1	3	1	31
NSAIDs and nonopioid analgesics	3	6	11	2	1	1	–	24
Antidepressants	3	7	6	5	–	1	–	22
Tuberculostatics	4	7	3	1	–	–	–	15
Antibiotics	2	7	–	2	–	–	–	11
Acetaminophen	3	2	2	2	1	–	–	10
Drugs and other substances	2	–	4	2	1	1	–	10
Hypoglycemiant agents	2	1	2	1	1	–	–	7
Opioids	4	1	–	–	–	–	–	5
Unknown drugs	8	20	17	11	4	7	3	70
Total	132	242	201	104	72	36	24	811

On average, the cases arrived in the clinic at 6.42 ± 7.80 hours from ingestion. The raised value of standard deviation indicates the higher variability of the parameter in our group. The patients were hospitalized for 3.12 ± 2.39 days, the longest hospitalization period being registered for neuroleptics poisoning, 4.04 ± 3.41 days. From all patients, 20% were admitted in the intensive care unit.

In the majority of cases, the patients were released with a referral towards a psychiatric consult (82.16%). There were registered cases of release on request (14.96%), against the doctors' recommendations and warnings about possible complications. In only two of the patients surveyed the outcome was death (one with barbiturates and one associating barbiturates with phenothiazines), representing 0.3% of the cases. Both patients were men, from urban areas, between 31-40 years old, on the first attempt, which associated alcohol intake. In both patients, blood alcohol levels were higher than 300 mg/dl. The inter-rater score for categorical variables varied between 0.92 and 1, expressing a good interrater reliability.

Results of the third epidemiological study

A total number of 606 patients were included in the epidemiological study concerning CIS poisoning, counting for 11% from the total number of acute poisonings. We summarize the results in the Table III.18 for the easier comparison.

The highest numbers of cholinesterase inhibitors poisoning cases were hospitalized in 1995 (44 cases). Distribution of the cases number per year is observed in Figure III.24. From the total number of cases, 342 (56.4%) were females and 264 (43.6%) were males. The highest percent of cases (25.4%) were from the age group 20-29, followed by 30-39 (20.8%) - Figure III.25.

Most of the cases came from rural areas (404 – 66.7%), 28.2% being agricultural workers. The most common route of poisoning was oral (92.2%), only 2.5% dermal exposures and 2.1% inhalation. The reason for exposure was intentional in 70% of cases and accidental in 30%. In a majority of cases (90.1%) the cholinesterase inhibitors agents were unknown. In

5.6% of cases poisoning was a result of an association of toxins, pesticides and drugs, predominantly sedative-hypnotics. Alcohol intake was associated in 38.6% of cases. The mean volume of CIS solution that was ingested was 77.40 ml.

The amount ingested was bigger in male patients (90.10 ml) than in female patients (68.69 ml) (p 0.004). Previous psychiatric disorders were reported in 4.3% of the cases while 5.8% patients had a history of suicide attempt. According to W.H.O. classification for severity of pesticide poisoning, 47% of cases were moderate and 36.6% were severe. Among severe clinical forms 55.9% of patients were female, predominantly from 30-39 age group (23%), followed by 20-29 age group (20.7%).

Among clinical forms, the mild forms were in almost equal percentage accidental (53.5%) or suicidal (43.4%). Moderate and severe forms were predominantly suicidal (70.5% and 81.1%). Severe forms were associated in 31.1% of cases with chronic alcoholism, the percentage being reduced in cases of mild (8.1%) or moderate forms (10.5%). 52.3% of patients presenting with severe signs and symptoms were associated with alcohol intake. Severe forms were accompanied by a more increased quantity of pesticide agent ingested compared with mild and moderate forms (p 0.004) and with more decreased serum cholinesterase on admittance ($p < 0.0001$).

Plasma cholinesterase on admittance had a mean value of 1.5 U/ml. The minimum value of serum cholinesterase was registered in the age group of ≥80, followed by 60-69 ($p < 0.001$) but without significant differences between genders (p 0.084). Serum cholinesterase mean values on admittance were more decreased in severe forms (1.0 U/ml) compared with mild (2.8 U/ml) and moderate forms (1.6 U/ml) ($p < 0.001$).

Table III.18. Summary of results of the retrospective study

Features		No. of Patients	Percent
Total No. of Patients		606	100
Sex	Females	342	56.4
	Males	264	43.6
Residence	Rural areas	404	66.7
	Urban areas	202	33.3
Occupation	Agricultural workers	171	28.2
	Non-agricultural workers	435	71.8
Reason for exposures	Intentional	424	70
	Accidental	182	30
Route of poisoning	Oral	559	92.2
	Dermal exposure	15	2.5
	Inhalational	13	2.1
	Mixt	19	3.2
Cholinesterase inhibitor substances (CIS)	Unknown	546	90.1
	Known (Neocidol, Detox, Sineparatox, Diazole, Neguvon, Parathion, Other CIA)	60	9.9
Association of other toxic substances	Alcohol intake	234	38.6
	Drugs (Sedative-hypnotics)	34	5.6
	Other substances	11	1.8
Medical history	No medical history	370	61
	Previous suicide attempt	35	5.8
	Psychiatric disorders	26	4.3
	Other comorbidities	175	28.9
Clinical forms	Severe	222	36.6
	Moderate	285	47
	Mild	99	16.4
Outcome	Discharged with medical recommendations	484	79.8
	Discharged on request	64	10.6
	Deceased	23	3.8
	Ran out of hospital	20	3.3
	Transferred	15	2.5

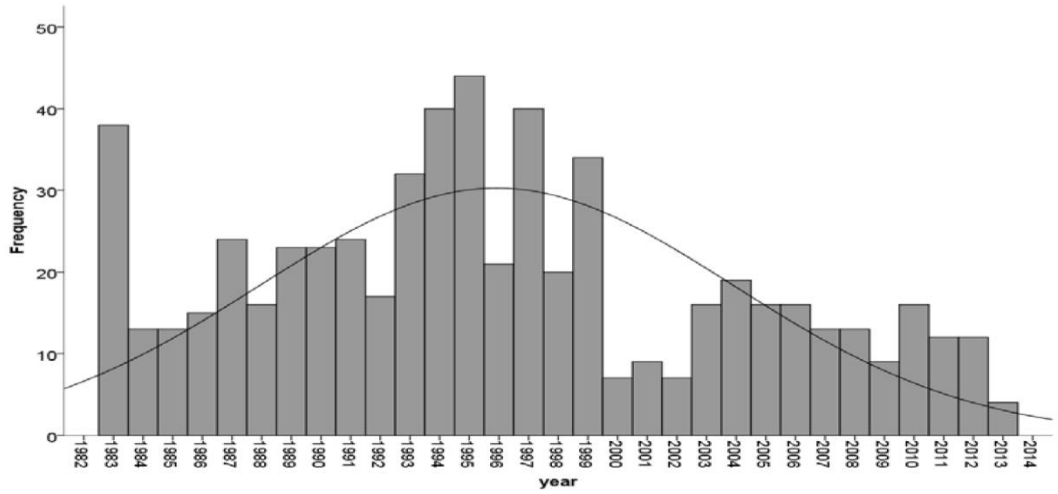


Figure III.24. Distribution of the cases number per year studied.

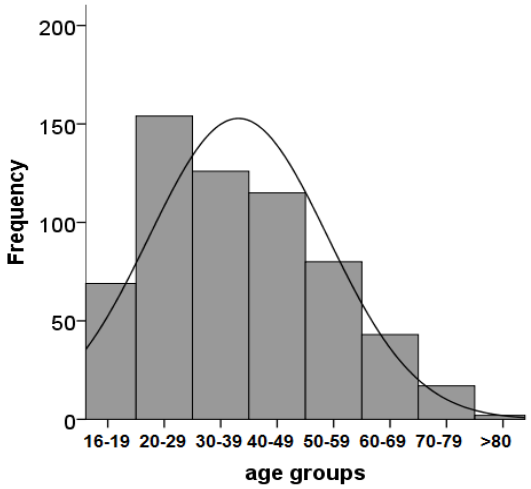


Figure III.25. Distribution of the patients in age groups.

Clinical features of cholinesterase inhibitors poisoning are presented in Table III.19. The most common sign or symptom was nausea encountered in 73.1% of cases, followed by sweating (71.8) and bronchial hypersecretion (71.3%). Possible factors responsible for poisoning were affective in 32.5% of cases and chronic alcoholism in 17.7%. The rest were either undeclared or an association of factors.

Gastric lavage was performed in 54.6 % (84%) of patients. The time interval between the poisoning moment and the hospital presentation was in average 8.78 hours. The increased value of standard deviation indicates the higher variability of the parameter in our group. Females arrived at the hospital 7.71 hours after poisoning and males 10.22 hours after the exposure, but the difference was not statistically significant (p 0.41). Complications occurred in 9.4% of cases, especially acute pulmonary edema and toxic myocarditis. In the majority of cases the patients were discharged with a medical prescription (79.9%).

Cases of release on request were registered (10.6%), before the end of the entire medical act, against the doctor recommendations and warnings about possible complications.

Table III.19. Clinical features of cholinesterase inhibitors substances poisoning

Clinical Features	Yes		No		Unknown	
	No. of Patients	Percent	No. of Patients	Percent	No. of Patients	Percent
Sweating	435	71.8	171	28.2	0	0
Miosis	356	58.7	250	41.3	0	0
Nausea	443	73.1	163	26.9	0	0
Sphincter Relaxation	109	18.0	496	81.8	1	0.2
Fasciculation	300	49.4	306	50.5	0	0
Bradycardia	81	13.4	525	86.6	0	0
Disorders of Consciousness	166	27.4	440	72.6	0	0
Bronchial Hypersecretion	432	71.3	174	28.7	0	0

Only 2.5% of the patients were transferred towards psychiatry for specific measures. Overall mortality rates were 3.8%. From the total number of deaths (23 cases) 82.6% were suicidal poisonings and only 17.4% accidental. More than half of the dead patients (65.2%) were associated with alcohol intake. Alterations in the patient's state of consciousness were the most common sign (73.9%) of presentation among the patient that died. It was a significant statistical association between the decrease of serum cholinesterase level on admittance and deaths ($p < 0.001$).

Discussion

We have documented a decreased incidence on IHN poisoning in our area, probably because of a better management of TB in our area, and the decrease, over the years, of the incidence of acute poisoning. The diagnosis of IHN overdose should be considered in any patient who presents with coma, unexplained metabolic acidosis and seizures (Temmerman et al., 1999). One study revealed that IHN was responsible for 5% of all cases of seizures associated with drug poisoning (Olson et al., 1993). The initial clinical picture can be easily confused with diabetic ketoacidosis (Romero & Kuczler, 1998). Differential diagnosis of a high anion gap metabolic acidosis should exclude poisonings leading to this metabolic alteration via a direct mechanism, such as salicylates and toxic alcohols poisoning, and those causing it via lactic acidosis, such as toxic gases, and strychnine. Also, conditions such as alcoholic ketoacidosis, starvation ketoacidosis, uremia, should also be excluded. Conditions associated with coma and seizures, including stroke, brain trauma, epilepsy, diabetes or other poisonings (i.e., organochlorine pesticides, tricyclic antidepressants, etc.) should also be excluded (Lionte et al., 2004). Rhabdomyolysis and IHN-induced hepatitis are complications that should be considered when caring for patients with acute IHN ingestion (Blowey et al., 1995). With adequate treatment and in the absence of complications, the prognosis is usually good in 24-48 hours (Alvarez & Guntupalli, 1995). At the early stage of the intoxication (1 to 12 hours), death is due to respiratory distress, and/or cardiac arrest secondary to acidosis and hypoxemia, or as a result of untreatable seizures. Deaths as a result of acute hepatitis or pancreatitis and post-anoxic coma have also been reported (Stewart et al., 1995; Jin & Sable, 2002). Patients with IHN poisoning should always be admitted to ED or ICU (Topcu et al., 2005). Supportive care with early mechanical ventilation, antidote administration – pyridoxine, and anticonvulsant drugs are indicated in severe poisoning with seizures. Only after pyridoxine administration and

supportive care, decontamination methods might be applied (Brent et al., 1990; Watkins et al., 1990; Tai et al., 1996; Siefkin et al., 1987).

During the 7-year period we have recorded acute drug poisoning, a number of 811 cases was analyzed, counting for 28.43% from the total number of acute poisonings. Consistent with the data from the majority of the studies from different countries (Akhlaghi et al, 2009; Mert & Gamsiz Bilgin, 2006; Chan et al., 1994; Fathelrahn et al., 2005; Sobhani et al., 2000; Kiyotaka, et al., 1998) suicide attempt was the most common cause of poisoning. There are considerable variations in the substances implicated in acute poisonings in different countries. In studies conducted in Poland, Spain, Taiwan, Turkey (Ankara, Istanbul, Mersin), Malaysia, Oman and different regions from Iran, the most common agent involved in acute poisoning were drugs, with variable sizes, between 42.7% in Spain and 89.34% in Western Iran from the total number of poisonings (Lee et al., 2008; Goksu et al., 2002; Jaraczewska & Kotwica, 1997; Özköse & Ayoglu, 1999; Tufekci et al., 2004; Hanssens et al., 2001). In the Romanian region we surveyed, the 28.43% drug poisonings were a result that aligns us with reports from Zimbabwe (30.4%), India (New Delhi 18.8%) and Thailand (19%), where the top leader in poisonings are the organophosphorus compounds (Tagwireyi et al., 2002; Srivastava et al., 2005; Chirasirisap et al., 1992).

The results of our study showed that the benzodiazepine group occupies the first place in acute drug poisonings, comparable with reports from Spain, Japan, Poland, different regions from Iran (Repetto, 1997; Ahmadi et al., 2010; Islambulchilar et al., 2009; Jaraczewska & Kotwica, 1997; Özköse & Ayoglu, 1999). Report from The American Association of Poison Control Centers, studies from North England, Paris/France, Turkey, Malaysia and Oman have shown that the most common agents involved were the analgesics (Bronstein et al., 2008; Goksu et al., 2002; Fathelrahn et al., 2005; Özköse & Ayoglu, 1999; Hanssens et al., 2001; Staikowsky et al., 2004; Thomas et al., 1996). In other reports, antidepressants or barbiturates were declared the most common drug poisoning agent (Bavunoğlu et al., 2004; Desalew et al., 2011). In our region, the frequency of analgesics poisoning follows psychotropic and cardiovascular drug poisonings. Benzodiazepines remain a constant leader in this Romanian region, displaying the highest percentage in a previous study accomplished in our clinic between 1991 and 2003, where from the 16,579 cases of acute poisonings recorded, 29.8% were drug poisoning, and from these the benzodiazepines represented 30% (Lionte & Sorodoc, 2005). More than half of the patients (65.88%) used only one drug, similar with other studies from Barcelona/Spain, Tabriz/Iran, Sari City/Iran, Istanbul/Turkey (Ahmadi et al., 2010; Bavunoğlu et al., 2004; Islambulchilar et al., 2009; Cirera et al., 1996).

The highest incidence was recorded in young adults, situation also reported by investigators from Iran and developing countries (Ahmadi et al., 2010; Lee et al., 2008; Akhlaghi et al., 2009; Fathelrahn et al., 2005; Lau & Liu, 1996; Eddleston, 2000). A slight predominance in women was observed, the male-to-female ratio 1:1.9. Comparable findings have also been reported in several studies conducted in Iran, Taiwan, Turkey and Hong Kong (Ahmadi et al., 2010; Lee et al., 2008; Goksu et al., 2002; Islambulchilar et al., 2009; Mert & Gamsiz Bilgin, 2006; Chan et al., 1994; Lau & Liu, 1996) but differs from epidemiological studies from the western part of Iran and India, where the poisonings are more frequent in men, possibly due to the religious characteristics in these regions, reasons actually mentioned by the authors (Shadnia et al., 2007; Srivastava et al., 2005; Ramesha et al., 2009).

Psychiatric disorders marked the history of 13.81% of the patients, percentage that is lower when compared with other studies (38.9%) in a Spanish multicenter study (Repetto, 1997).

Following the change that took place in the early 2000s in drug prescription regulations, in Romania psychotropic drugs are now released from pharmacies only based on medical

prescription. This explains the significantly small percentage in which psychotropic drugs originating from pharmacies were used as a means of suicide. Considering that a big proportion of the psychotropic drugs encountered in poisonings came from personal medication, we conclude that these patients had no records in a psychiatric care unit. The necessary prescription used to acquire these drugs was most probably prescribed by the family physician for sleep disturbances or minor anxiety disorders (Chan et al., 1994; Thomas et al., 1996; Desalew et al., 2011).

In our study, there is a delay between the ingestion and the admission time, similar with the reports from Izmir/Turkey, Helsinki/Finland and Hong Kong (Chan et al., 1994; Pinar et al., 1993; Lapatto-Reiniluoto et al., 1998). In contrast, in England the mean interval is 2 hours, in Tikur Anbessa/Ethiopia is 3 hours, and in a report from Spain 34.2% of patients come in the first 2 hours (Repetto, 1997; Thomas et al., 1996; Desalew et al., 2011). In our country, the delay is probably the result of the fact that mild forms of poisoning are treated first at home with a traditional antidote (milk, lemon).

Our study emphasizes the predominance of mild or medium intensity clinical forms. These usually associated a small number of pills ingested, young age, and required a reduced number of hospitalization days. Our results are in agreement with data reported by of Lapatto-Reiniluoto O. et al. in a 1998 Finish study. In most of these cases, the suicidal act of a patient with an unstable emotional profile is usually an attempt to engage the attention of the entourage and not a veritable lethal act. We have to note the increased use of alcohol, concomitant with a blood alcohol content higher than 150 mg/dl, fact also reported in studies from Finland, where two thirds of the poisonings involved alcohol, and from Taiwan where concomitant use of alcohol was recorded for 62.4% of the observed patients (Lee et al., 2008; Lapatto-Reiniluoto et al., 1998).

Our patients were hospitalized in average for 3.12±2.39 days, while the average hospital stay reported in literature was 1.5 days in studies from North Eastern England and Western Iran, 3.02 ± 2.8 days in Tabriz/Iran and 4 days in Karnataka/India (Akhlaghi et al., 2009; Islambulchilar et al., 2009; Ramesha et al., 2009; Thomas et al., 1996). The reduced mortality recorded by our study need to be remarked. This decreased mortality rate was described in epidemiological studies done in Japan in 1996 (12 cases of death from a total of 1188 acute drug poisonings, also related with benzodiazepines or barbiturates intake) or Northern Iran in 2008 (3 deaths from benzodiazepines poisonings in a total of 1598 cases of acute drug poisonings) (Ahmadi et al, 2010; Kiyotaka et al, 1998). The fatal outcome was registered in our group in men, like in another study from Belgium, with male to female ratio of 9:1 (Bruyndonckx et al., 2002).

The current research entailed certain limits, the fundamental problems being that it was a hospital-based study and the population under 18 years of age was not included. Yet, through the significant numbers of patients considered, over a 7-year span, we believe that our research provided significant information concerning the pattern of acute drug poisonings in North-Eastern Romania.

Our research on CIS poisoning provides the first comprehensive analysis of the cholinesterase inhibitors poisoning in this region. The analyzed data indicate that CIS exposures represent only 11% of the total number of hospitalized poisonings. Intentional pesticide poisoning exposure accounts for most of the poisoning cases. A retrospective study from China with a total of 20,097 pesticide poisoning cases showed that suicide was the most common reason for poisoning (Zhang et al., 2013). Other similar data come from Sri Lanka, India, South Korea and Nepal (Eddleston et al., 2006; Kora et al., 2011; Dash et al., 2005; Kim et al., 2012; Chataut et al., 2011). An article which has systematically reviewed the worldwide literature to estimate the number of pesticide suicides in each of the World Health

Organization's six regions concluded that pesticide self-poisoning is one of the most commonly used methods of suicide worldwide, and it accounts for about one-third of the world's suicides (Gunnell et al., 2007). In developed countries such as United States and Sweden accidental poisoning is the leading cause of pesticide-related hospital admission (Klein-Schwartz & Smith, 1997; Persson et al., 1997). We find that most of the cases were from rural areas but only 28.2% were agricultural workers. These data suggest a far too easy pesticide access for people without training or license use and improper storage facility.

The present study reveals the predominance of females. In other studies, male predominance has been reported (Kim et al., 2012; Badakhsh et al., 2010; Lamminpaa & Riihimaki, 1992). This may be explained by non-occupational type of poisoning. Almost half of the cases were young patients (aged 20-39) with a peak at 20-29 years of age. This pattern is similar with that reported from different other developing countries such as Costa Rica and India (Wesseling et al., 1993; Murali et al., 2009). A different profile results from a survey from South Korea (Kim et al., 2012). In this research, pesticide-related hospitalization increased with age, with the highest rate noted among those aged 70 or above. China and Japan have the same high suicide rate by pesticide poisoning in elderly people, compared with that in young and middle-aged adults (Zhang et al., 2013; Nagami et al., 2005). The major limitation of our study is that we only included pesticide poisoning in adults aged over 16. Actually, children are an important group for self-harm through pesticides in some regions. Data from Minnesota, North and South Carolina and Milan, Italy showed that the mean age of all reported instances of pesticide poisoning (adults and children) was 5 years (Garry, 2004).

The most common clinical finding in our study was nausea followed by sweating and bronchial hypersecretion. Comparison of the clinical features observed in the present study with other studies showed that nausea is the most common symptom in all the studies, but bradycardia and miosis were more often encountered in other studies (Banerjee et al., 2012; Rehiman et al., 2008). We have to note the concomitant use of alcohol in many patients, fact also reported in our study regarding drug poisoning, meaning that efforts to reduce self-poisoning may benefit from concurrent efforts to reduce alcohol consumption (Sorodoc et al., 2011). Associated alcohol use is also reported in Sri Lanka (Eddleston et al., 2006).

A small percentage of patients had history of psychiatric disorders; however, an important reason for attempted suicide was affective disorders. Also, not too many patients were transferred towards a psychiatric department. In literature, most cases had a history of mental illness, mostly depression followed by personality disorder as documented in almost all the studies reviewed by research done in a tertiary hospital (Risal et al., 2013). Similarly, findings in the Risal study, such as marital disharmony, family conflicts, economic hardships and family disputes, were the major precipitating factors for the act in the studies from United Kingdom and Greece (Haw et al., 2001; Exiara et al., 2009). Severe forms are correlated in the present study with intentional poisoning, an increased amount of CIS and decreased level of cholinesterase. The reason of having butyrylcholinesterase (BuChE) as main specific test for cholinesterase inhibitors substances poisoning relates to the fact that in Romania, due to accessibility reasons, this was the most frequently used test. Also, plasma cholinesterase is easier to assay and is more readily available.

Acethylcholinesterase tests even more sensible are also not so much used in daily clinical activity. The usefulness of BuChE activity measurement upon admission to stratify severity in acute insecticide poisoning has been debated for long. Some studies showed that plasma BuChE activity on admission can provide useful information but it must be interpreted critically with definite knowledge of the ingested CIS (Eddleston et al., 2008). Overall, a BuChE activity on admission is only useful when the CIS pesticide has been identified and when its sensitivity and specificity is known for that particular pesticide.

In our study the patients came late to the hospital, in average 8.78 hours, however the gastric lavage was performed in more than half of the patients. Gastrointestinal decontamination with gastric lavage is now used less often in the hospital setting because there is currently no high-quality evidence to support its clinical effectiveness in pesticide poisoning (Li et al., 2009). Additionally, the importance of iatrogenic deaths caused by inappropriate gastric decontamination as shown by the number of deaths occurring after ingestion of low toxicity pesticides needs to be emphasized (Eddleston et al., 2007). Despite extensive evidence demonstrating little benefit and significant risk of gastric lavage in the management of poisoned patients, it is still extensively used in Romania, like in other regions from Asia (Li et al., 2009; Naderi et al., 2012). We consider this decontamination method still useful based on its simple technique, reduced cost and effectiveness in the first few hours post ingestion.

Overall mortality rates were 3.8%. The majority of the cases were suicidal poisonings, presenting with an altered mental status, decreased level of serum cholinesterase upon admittance and more than half of the deceased patients were having associated alcohol intake. This decreased mortality rate was described in epidemiological studies done in India and Morocco (Kora et al., 2011; Rhalem et al., 2008). Other studies from South Korea and Taiwan reported increased mortality probably in relation with utilization of WHO Pesticide Hazard Class I OPs (Lin et al., 2008; Kim et al., 2012). Alcohol co-ingestion is known to be associated with higher plasma concentrations of some CIS and increased risk of death (Eddleston et al, 2009). Also, decreased concentrations of plasma cholinesterase was considered a factor for increased mortality in a previous prospective case series study (Lin et al., 2007).

Conclusions

We have noticed a decreased incidence of acute INH poisoning probably because of a better management of TB in our area, and of a decrease in the total amount of acute poisonings. Acute INH toxicity should be suspected in patients presenting with seizures, coma and metabolic acidosis. In patients with a known access to INH, we must consider seizures to be caused by INH toxicity unless proved otherwise. Parenteral pyridoxine, the specific antidote for INH-induced seizures, should be readily available in every emergency department.

Sedative and hypnotic drugs occupied a preferred position in the main drugs used in suicide attempts in our region. This emphasizes the necessity for a better stipulated algorithm under which these drugs are prescribed and released from pharmacies. We should avoid prescribing such medicines when it is not absolutely necessary and try to prevent an accumulation of pharmaceuticals available for suicidal purpose at patient's home. Based upon the high number of patients that resort to repeated suicide attempts, it becomes clear that a coordinated effort to integrate the intervention of a toxicology expert with a psychiatrist is necessary (Taylor et al., 1998). One strategy to reduce CIS poisoning cases is to restrict the availability and accessibility of toxic pesticides, adopting a non-pesticide management policy.

Considering the long delay between the moment of the ingestion and the time of the arrival in the toxicology clinic, we conclude that a better continuous medical education on this subject is necessary, tailored on targeting an early admittance of poisoning patients in a medical unit (Sharma et al., 2002). The second approach to reduce CIS poisoning is to improve educational measures regarding the danger of pesticide poisoning and safekeeping of pesticides.

The information we recorded tends to show that the highest risk profile for acute drug poisoning is young, unemployed, woman and the most frequently involved drugs are benzodiazepines. The pattern of poisoning described by our study suggests that CIS poisoning is mainly preventable. These data underline that, in order to provide a proper management of drug poisonings, a Regional Poison Information Center is absolutely necessary.

SECTION II.

DIRECTIONS FOR THE DEVELOPMENT OF SCIENTIFIC, PROFESSIONAL, AND ACADEMIC ACTIVITY

A clinician working in an emergency university hospital needs professional expertise and performance for at least two main reasons. First, the patients addressed to such a teaching hospital have complex pathologies, which need serious knowledge and a mindset capable of making vital decisions, especially in emergency circumstances. Second, one needs clinical maturity, essential for cooperation with specialists in other domains, young residents or students. My double specialty, in internal medicine and cardiology, along with the expertise in the field of clinical toxicology, allowed an extensive approach of various research themes.

My scientific and publishing effort in the last twenty years, in the post-doctoral period, covered six main directions: fundamental research of experimental toxicology; clinical research in internal medicine and toxicology; multimodality imaging studies in patients with medical or toxicological emergencies; observational studies involving acute poisoning; development of risk models to assess the outcomes in hospitalized patients; publishing manuals and textbooks in the field.

The COVID-19 pandemic, and the fact that our department was actively involved in the management of patients with SARS-COV2 infection, changed our daily activity, in the internal medicine department, and as a result, also our research initiatives.

At this moment, I intend to develop my clinical research preoccupation into the following directions:

- Influence of COVID-19 pandemic on the pattern of medical emergencies, including acute poisonings in North-Eastern Romania.
- Identification of new risk-predictors and scores useful to improve the management of patients with medical conditions and SARS-COV2 infection.
- The role of vitamin D in inflammatory and cardiovascular diseases.
- Studies regarding multimodality diagnostic methods and the role of modern therapies in patients admitted for medical emergencies.

Also, I will continue to explore the subjects which were my main research preoccupation in the past twenty years, such as cardio-metabolic interrelations in patients with cardiovascular conditions and/or cardiovascular risk, the biomarkers in poisoned patients and those admitted with a medical urgency and emergency as well as new and emerging imagistic techniques and therapies for medical patients, taking into account the potential influences exerted by our therapeutic intervention.

In the next pages, I will detail the scientific research I intend to expand in the upcoming period.

II. 1. Scientific activity

II.1.1. Considerations supporting research in the field of pattern of the medical emergencies.

Some studies have suggested a change in the number of hospital presentations and/or the severity of acute illnesses requiring urgent management during the pandemic. The exact causes of these findings remain to be determined. The impact of the COVID-19 pandemic on the number of suicide attempts or on the incidence of mental illness has not been well addressed yet (Vindegaard & Benros, 2020).

A few studies have reported an unusual increase in exposure to the xenobiotics used to protect against COVID-19 infection. In Iran, 700 people died from misusing denatured alcohol containing methanol, which was thought to be an alternative treatment to protect against COVID-19 infection (Mehrpour & Sadeghi, 2020) and 22 fatalities among children and adolescents were recorded during the first COVID-19 pandemic wave (Mahdavi et al., 2021). In the United States (US) and in France, Poisoning Control Centers (PCCs) have been warned of a possible increase in cases of poisoning due to disinfectants and cleaning products (Chang et al., 2020; Le Roux et al., 2020).

A French study from February 2021 showed both quantitative and qualitative changes in calls to French PCCs during the lockdown period of the COVID-19 epidemic. Both the pattern of exposed patients and the pattern of exposures were altered. Overall, exposed patients were younger, although relative increases in exposures were larger among older adults. Accidental home exposures increased while workplaces and school exposures and recreational/suicidal exposures decreased. Home cleaning products, alcohol-based hand sanitizers, and essential oils exposures increased while pharmaceuticals exposures decreased. Despite the increase in exposures, the incidence of symptomatic exposures remained stable with a decrease in severity (Le Roux et al., 2021).

A Spanish study which involved two centers analyzed the emergencies over three years, and concluded that the number of intoxications with drugs had increased in 2020 by 31.3%, and reported a decrease of poisoning with recreative drugs by 8.8%, although the proportion of intoxications within the total amount of emergencies remained stable. The explanation was the limited mobility and quarantine, which led to a tendency towards self-harm or ingestion for anxiolytic purpose (Puiguriguer-Ferrando et al., 2020).

A study conducted by the European Monitoring Centre for Drugs and Drug Addiction indicated that the use of illicit drugs decreased by almost 50%. In descending order, the four most frequent reasons for the decrease in illicit drug use were fewer opportunities to use them, reduced availability of illicit drugs to buy, reduced ability to collect them, and loss of available income to buy them (EMCDDA, 2020).

Similarly, in Taiwan, there was a trend towards venomous animal or plant induced injury's decline, which also correlated to the tightness of epidemic control measures, but an increased number of suicidal overdoses resulted from mental stress of quarantine fear, anxiety to pandemic, alienation from people and economic recession (Tan et al., 2021).

Off-label administration (the use of an approved medication for an unapproved use) has the least regulatory oversight and requirement for structured data collection. Chloroquine, hydroxychloroquine, and azithromycin have been used in this manner with mixed but generally negative results (Farmer et al., 2020).

Public health measures to counter the COVID-19 pandemic reduced the need for ED care by curtailing the spread of other infections and altering the epidemiology of emergencies. It will be important to track the incidence of these conditions to determine whether these have been altered by SARS-CoV-2 infection or measures designed to stem the COVID-19 pandemic. The changing pattern of acute poisoning may affect complications and outcome in these patients.

The study on epidemiologic changes of poison exposures in our region during pandemic period will involve teamwork, with very close collaboration with the pediatricians, internal medicine and emergency medicine specialists from different emergency hospitals in North-Eastern Romania. The study will be possible due to my earlier experience with epidemiological studies.

II.1.2. Considerations supporting clinical research in the field of risk scores.

The COVID-19 pandemic focuses on respiratory manifestations, but evidence has emerged relative to major cardiovascular implications. Preexisting cardiovascular conditions increase risk for COVID-19 and also for cardiovascular manifestations sometimes leading to death. Understanding this aspect is imperative for the internal medicine community. Given the extent and variability of cardiovascular manifestations, the care of these patients is challenging and includes direct virus effects and possible iatrogenic effects from treatments. Our experience in the early pandemic period proved that the association with VTE as a comorbidity, fever, dry cough, and myalgias as clinical features, and GGO as a CT aspect are the main significant markers for the differentiation of patients with acute clinical syndromes suspected of having SARS-CoV-2. These data are useful for faster decision-making in the triage of COVID-19 patients before receiving RT-PCR test results, which can aid in avoiding keeping patients in crowded emergency departments (Haliga et al., 2021).

During this period, several research papers attempted to identify predictors of critical care admission and death in people admitted to hospital with COVID-19. Reported demographic predictors for developing severe COVID-19 included older age and male sex. Clinical predictors of severe COVID-19 included abnormal neutrophil and lymphocyte counts, elevated CRP, and computed tomography findings. Ethnicity differences in outcomes were widely reported and non-white ethnicity predicted critical care admission (Galloway et al., 2020).

A risk score based on characteristics of COVID-19 patients at the time of admission to the hospital was developed that may help predict a patient's risk of developing critical illness, based on chest radiographic abnormality, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase and direct bilirubin (Liang et al., 2020).

A quick prediction nomogram was developed by Chinese authors (Figure II.1.), composed of age, direct bilirubin, red blood cell distribution width–coefficient variation, blood urea nitrogen, C-reactive protein, lactate dehydrogenase, and albumin. It was validated to identify and predict COVID-19 patients at risk of severe disease (Gong et al., 2020).

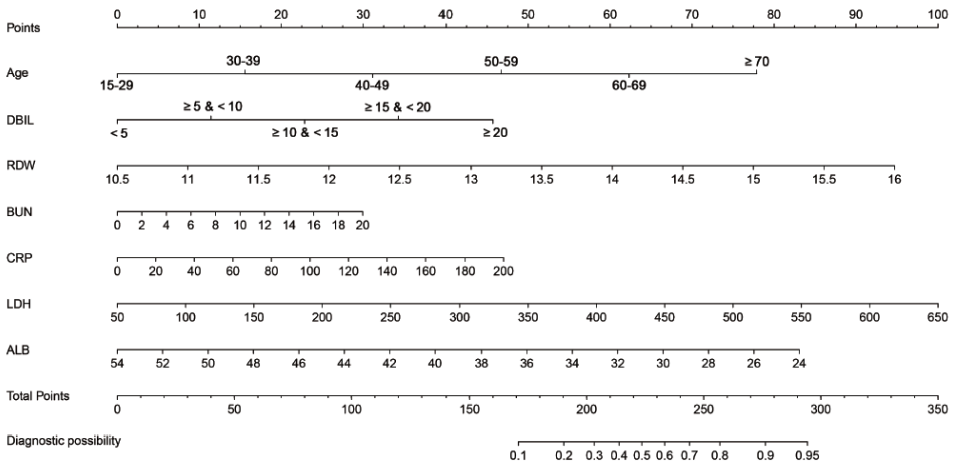


Figure II.1. A prediction nomogram in patients with coronavirus disease 2019.

Other authors incorporated in their risk-model exclusively the explanatory variables that were directly related to the pathogenesis of COVID-19, such as SpO2 <95%, neutrophil

and platelet count upon admission, CRP and LDH, and proved that patients can be assigned a probability of critical disease or fatality on the basis of information from the initial history and quickly available laboratory examinations (Salto-Alejandre et al., 2021).

Given the fact that we mainly provide care for patients with an acute medical emergency and associated comorbidities, the aim will be to help clinicians rapidly identify which patients, attended for the first time in an emergency room and regardless of their age, sex, or comorbid conditions, are more likely to be transferred to the intensive care unit (ICU) or to die, and are therefore candidates for a close monitoring and for the administration of the best available therapy. Thus, we will focus on the simplest and readily available hemodynamic and laboratory features to build a quick prognostic equation that, based on independent predictors, will be able to estimate the probability of ICU admission or death among adult COVID-19 inpatients. The findings will help inform admission and discharge decisions, providing frontline clinicians with a tool to identify patients most at risk of deterioration. The COVID risk score may help identify patients with medical emergencies and COVID-19 who may subsequently develop critical illness.

This area of research will involve inclusion of PhD students in collecting data, and a very close collaboration with the specialists in medical statistics, internal medicine, infectious disease, pneumology and emergency medicine from different departments involved in the assistance of COVID-19 patients. The study will be possible due to accumulated experience in the field of nomograms' development.

II.1.3. Considerations supporting clinical research in the field of vitamin D.

To begin with, I've contributed to an extensive review of literature, presented below, about the role of vitamin D deficiency in systemic sclerosis and emphasizing the association of vitamin D status with different clinical settings.

Efforts to assess the vitamin D status of populations in low- and middle-income countries have been hampered by limited availability of population representative 25(OH)D data, particularly among population subgroups most vulnerable to the skeletal and potential extra skeletal consequences of low vitamin D status, including the elderly. Inflammation has been shown to slightly reduce 25(OH)D (Roth et al., 2018). However, details on the interference between low serum vitamin D levels and pathogenesis of these conditions remain controversial in some aspects, and future studies are needed to clarify this involvement.

Strong evidence emerged linking vitamin D deficiency to adverse respiratory outcomes, particularly asthma exacerbations (Brehm et al., 2012) and tuberculosis reactivation, likely mediated by the immune modulatory effects of vitamin D (Roth et al., 2018). Given the growing understanding of the established links between vitamin D status and the incidence of respiratory infections and asthma, it is important to pursue further research to address the most critical gaps in knowledge regarding this micronutrient and to generate accurate information about the prevalence of vitamin D deficiency in our region.

An important segment of patients who are admitted in our department from ED are the elders. Long-term cognitive impairment, defined as new or worsening deficit in cognition that persists following acute illness, is a well described phenomenon occurring in an estimated 16% of older adults who are acutely ill (Phelan et al., 2012). The relationship between vitamin D deficiency in the setting of acute illness and subsequent development of cognitive impairment remains poorly characterized in acutely ill patients, although vitamin D deficiency was proved to be associated with poorer six-month cognition in acutely ill older adult ED patients who were cognitively intact at baseline (Evans et al., 2019).

A possible association between rhabdomyolysis patients admitted to ED in an acute alcohol-intoxicated state with vitamin D deficiency was shown (Lee et al., 2019). Some authors have pointed out an association between vitamin D deficiency and alcohol-induced myopathy (Arik et al., 2016; Wijnia et al., 2013). Given the earlier research in the field of nontraumatic rhabdomyolysis, I am confident that this direction can be pursued in our department.

Therefore, an area of research to determine whether serum vitamin D at ED presentation in patients admitted for medical emergencies, and the correction of the deficit might have a role for the outcomes of these patients admitted for an acute illness. An interdisciplinary team will be the solution for many issues in this area of research.

II.1.4. Considerations supporting clinical research in the field of multimodality diagnostic methods and modern therapies in patients with medical emergencies.

Given my specialty in cardiology, I was preoccupied on research regarding multimodality imagistic diagnosis and biomarkers in patients with acute poisoning, heart failure, peripheral artery disease and cardiovascular risk factors as well as asymptomatic heart disease, and the results were presented both in published original papers and in abstracts submitted to prestigious journals. I intend to continue my research started in the field of traditional and new biomarkers, and expand the categories of medical emergencies where they can be beneficial for early triage, diagnosis and therapeutic decisions.

As to the ongoing ED crowding worldwide, an effective management for patients with medical emergencies is mandatory (Gallagher et al., 2017). Ideally, optimization of patient management and resource allocation should be based on a time and cost-effective risk stratification (Afilal et al., 2016). Our research team recently proposed that the combination of a biomarker approach might improve existing risk stratification tools in patients with medical emergencies (Stoica et al, 2019).

Earlier risk stratification has the potential to reduce time to effective treatment - a main predictor for patient outcome across different medical conditions, including sepsis (Puskarich et al., 2011), pneumonia (Kumar et al., 2006), stroke (Adams et al., 2008), and myocardial infarction (Cantor et al., 2009). International guidelines recommend the use of risk scores in well-defined patient populations such as the Pneumonia Severity Index (PSI) in community-acquired pneumonia (Fine et al., 1997).

Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are established prognostic markers for outcome and mortality in various fields of cardiovascular (CV) disease (Fonarow et al., 2007; Kragelund et al., 2005; Hijazi et al., 2012). Cardiac troponins are sensitive biomarkers for cardiac damage and already slight elevations are associated with adverse outcome in CV disease (Resl et al., 2016; Omland et al., 2009). For patients with atrial fibrillation, which represent a majority of the medical emergencies admitted to our department, a biomarker-based approach might prove helpful for the identification of patients at increased risk for mortality during mid-term follow-up (Kirchhof et al., 2016). Improved assessment of the pathophysiological process involved in the individual patient by using clinical characteristics, blood biomarkers, and non-invasive substrate determination using multimodality imaging techniques (echo/MRI/CT) may improve personalized therapy (Hindricks et al., 2021).

Many other biomarkers have been related to risk in selected ED patient populations, including the prognostic inflammatory marker pro-adrenomedullin ([a]Schuetz et al., 2015; Suberviola et al., 2013; Courtais et al., 2013), the stress marker pro-vasopressin or copeptin (De Marchis et al., 2013; Potocki et al., 2010; Kruger et al., 2010) and the bacterial infection marker procalcitonin (Zhydkov et al., 2015; Hottenrott & Schummer, 2013).

There is a lack of a more general risk stratification score for undifferentiated medical patients at the most proximal time point of seeking ED care. At this earliest time point in ED care, risk stratification is most challenging due to lack of thorough clinical information, but may have the biggest potential to reduce time to effective treatment of patients and to improve patient flow. In addition to triage scores, there is high potential in the use of prognostic biomarkers from distinct biological pathways to identify persons who are at risk for high treatment urgency and adverse medical outcome ([b]Schuetz et al., 2015). Combination of clinical information with results of blood biomarkers measured upon ED admission allows early and more adequate risk stratification in individual unselected medical ED patients. For instance, according to our observations, NT-proBNP, hs-TnT and galectin-3 may serve as those ideal biomarkers for identification of patients with acute medical condition a risk (Rotariu et al., 2019; Lionte et al., 2017); due to the increased risk of all-cause mortality, an extensive screening of some biomarkers simultaneously (a "multi-marker" approach) in unselected ED patients could enhance early risk stratification. The potential of early triage to improve patient flow, treatment times, medical outcomes and costs needs to be assessed in an observational study. The research will be possible due to accumulated experience in previous studies of biomarkers in ED, and will involve a multidisciplinary team, with the active participation of PhD students.

II. 2. Professional activity

The development of professional skills is closely related to the scientific activity that I intend to conduct for the foreseeable future. For this reason, along with maintaining the interdisciplinary relationships developed over time, I aim to improve my cooperation with other medical specialties, present in our emergency hospital. I will continue to encourage residents (potential PhD students) to access the imagistic investigation available in our department, as a tool useful to complete the physical examination of a patient. I will continue to inspire them to take part in clinical studies and reporting their work in published papers or in medical congresses, local and abroad.

II. 3. Academic activity

The continuous improvement of the teaching methods and skills for students and resident physicians will be one of my main academic projects. I have plans for reediting and updating the internal medicine and toxicology manuals for Romanian and English Program students published alongside with my colleagues. I will continue to contribute, alongside with the residents I coordinate, to the publishing of a second edition of "Internal Medicine – from case to case", which represents a useful tool for education of my young colleagues in difficult clinical scenarios. I am considering the preparation of a new facultative course direction, for medical students, concerning interdisciplinary topics, such as the management of critically ill medical patients, new therapies in internal medicine, etc. I consider useful, in this regard, to propose a re-initiation of the master program in Clinical toxicology.

Since I will be involved in a new phase of coordinating PhD students, I now see the need for a selection of my PhD students among the worthy residents with performances and a broad vision regarding their professional development, who will be willing to pursue a multidirectional career, as the one in the academic field definitely is. Therefore, the widening dimension of my research team in mandatory, where the young PhD students will be encouraged to increase their professional autonomy, under the surveillance of more experienced members of the team. Thus, the PhD students in projects of my research team will

have the opportunity to gain a visibility of their own in various journals, and in national and international scientific conferences. An important issue is the continuous improvement of the quality of research provided by the team I am part of, and the acquirement of a wider international recognition, by publishing in more and more performant journals. The expanding interdisciplinary dimension of the research team I am part of will be achieved after incitement of PhD students from other medical specialties to actively participate in our research directions. For this reason, I will continue to develop the high level of academic interaction I have been establishing in the last years.

I will make efforts to access funding sources, such as research grants from UEFISCDI, international grants from several funding agencies, including the professional organizations such as the European Society of Cardiology, or pharmaceutical companies, to finance the projects important for my scientific development plans.

II.4. Conclusions

This habilitation thesis presents the main professional, academic and scientific achievements of my career, over the postdoctoral period (2003-2021), and few of the projects I have for my future development in the scientific, professional, and academic fields. Based on the experience I've already gained, I will continue to explore the major scientific topics which represented my main preoccupation during this period, and I will move toward new clinical research topics centered upon medical emergencies and cardiovascular diseases.

Obtaining the habilitation certificate represents a prestigious step in my academic career, and a recognition of my efforts to improve the education of students and residents in internal medicine and clinical toxicology. Also, I consider it to be an appreciation of the endeavors I undertook to increase the international prestige and visibility of the University of Medicine and Pharmacy "Grigore T. Popa" Iasi. This degree will offer me the premises to obtain the highest academic rank, as professor in internal medicine, and will allow the opportunity for upbringing the young teaching assistants and researchers in the discipline, department and university to which I belong.

SECTION III.

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