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BIOANALYSIS OF THE DESIGNER BENZODIAZEPINE FLUBROMAZEPAM

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Benzodiazepines are psychoactive drugs widely used in the treatment of anxiety, insomnia, agitation, seizure, epilepsy, but there is also a widespread misuse of these drugs. Since 2012, designer benzodiazepines appeared on the illegal market as non-prescribed drugs, taken for recreational purposes or as "self-medication" by users addicted to stimulant and hallucinogenic drugs of abuse. Most recently, the designer benzodiazepine flubromazepam started to emerge in online shops. There is very limited data about flubromazepam with regard to pharmacological properties, metabolism and possibility of detection in biological samples. This study focuses on the bioanalysis of flubromazepam in a mixed intoxication by flubromazepam and metoxyphenidine. **Case report:** A 25 years-old man was admitted to the emergency department twenty hours after an episode of syncope with secondary head trauma. On arrival, he presented severe psychomotor agitation, confusion, dysarthria and aphasia, mild hypertension and slight tachycardia. The patient's parents lead some pills and a powder bought on the Internet and labeled, respectively: flubromazepam and 2-methoxphenidine. The patient was discharged two days later with prescription of paroxetine. Toxicological analyses: Urine and serum collected on the day of hospitalization, as well products found by parents, were submitted to the Laboratory for toxicological analyses including screening for classical drugs of abuse and benzodiazepines by immunoassay (Syva EMIT II Plus) and new psychoactive substances using mass spectrometry-chromatographic techniques (GC-MS and LC-MS/MS). **Results and Discussion:** The gas chromatography-mass spectrometry analyses (GC-MS) of the products confirmed the presence of the declared analytes: flubromazepam and 2-methoxphenidine. Immunoassay for benzodiazepines in urine was under the cut-off concentration (178 ng/ml VS cut off 200 ng/ml lormetazepam equivalents) in the untreated sample and tested positive (378 ng/ml) after hydrolysis with beta-glucuronidase. The cross-reactivity of the flubromazepam with the used immunoassay resulted of 166 %. Urine and blood LC-MS/MS analyses excluded the presence of other benzodiazepines besides flubromazepam: urine flubromazepam concentration after enzymatic hydrolisis was low as 4 ng/ml, consequently it could be postulate that positivity to the benzodiazepines urine immunoassay test may be due to the cross-reactivity of flubromazepam metabolites[1]. Flubromazepam serum concentration (LC-MS/MS) tested 247 ng/ml, a value higher than the one measured as Cmax, after a single oral dose of 4 mg taken by a volunteer who experienced some fatigue and somnolence[2]. 2-methoxiphenidine quantification in serum (LC-MS/MS) yielded a concentration of 411 ng/ml. **Conclusions:** Flubromazepam can be specifically detected in serum and urine by LC-MS/MS. The unchanged drug in urine was present at low concentrations and Syva EMIT II Plus benzodiazepines assay resulted positive after enzymatic hydrolysis, likely exploiting metabolites cross-reactivity.

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DEXRAZOXANE FOR RAPID EXTENDED LIVEDO RETICULARIS-LIKE SKIN REACTION DUE TO SYSTEMIC EPIRUBICIN DIFFUSION DURING TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION FOR HEPATOCELLULAR CARCINOMA

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Background: Skin reactions after transcatheter arterial chemoembolization (TACE) with anthracyclines is a rare complication of intra-arterial chemotherapy infusion[1]. Most reactions are limited to small areas and no data concerning the use of dexrazoxane to treat skin reactions due to systemic diffusion of anthracyclines after TACE are at our knowledge reported. We describe a case where an extended livedo-reticularis-like reaction developed after TACE procedure with epirubicin for hepatocellular carcinoma (HCC) chemoembolization therapy and has been successfully treated with dexrazoxane. **Case report:** A 56-year old man with hepatitis C-related cirrhosis received one session of conventional TACE to treat one nodular HCC in segment 1. Hematological and hepato-pancreatic exams before the procedure resulted normal. TACE was performed through left hepatic artery catheterization and

super-selection of the segmental artery feeding the HCC followed by infusion of ethiodized oil and epirubicin 50mg. A further infusion of ethiodized oil, epirubicin 25mg and 40-micron-sized embolizing microsphere was performed through an anatomical variation characterized by a HCC afferent artery starting from the right renal artery. Immediately after the procedure the patient presented pain on the right side associated to a livedo reticularis-like skin reaction extended from right flank to hypochondrium areas. NSAID, opioids, chlorpheniramine iv were unsuccessfully administered. A possible adverse reaction due to epirubicin systemic diffusion was suspected so antidotic therapy with dexrazoxane 1000mg/m2 body surface was administered 8 hours after the procedure followed by 1000mg/m2 on second day, 500mg/m2 on the third day. Laboratory course presented hepatic tests peak on second day (ALT 443U/L, AST 1189U/L), increased d-dimer (14459 ng/mL) on fourth day, decreased platelets ($22.0X10^9$/L) on eighth day. On the fourth day abdomen CT evidenced hyperdensity in right lower pulmonary lobe, right hepatic segments, diffused thickening of the right abdominal wall and right hemidiaphragm with right basal pleural effusion. The patient underwent thoracic drainage from the 6th to the 18th day, received blood transfusion and granulocyte-colony-stimulating-factor on the seventh (hemoglobin 8.6g/dL, leukocytes $1.07X10^9$/L, neutrophils $0.49X10^9$/L). Skin presented a complete resolution at one month after TACE. During the third and fourth week from TACE the patient presented reduction of the abdominal pain, a progressive improvement of the right pleural effusion and normalization of hematological and hepatic parameters. Alopecia manifested on 21st day as a late systemic effect of epirubicin. No alterations in heart function were evidenced. **Discussion:** Adverse skin reactions related to anthracyclines systemic diffusion during TACE are mostly nodular spotted-like skin eruption limited to peri-/supra-umbilical areas with time onset of 1-30 days and time resolution up to several months after the procedure [1]. The diffused and rapid onset of skin picture in our patient is possible due to a rapid diffusion of epirubicin into superficial skin abdominal arteries through hepatic falciform artery and anatomical variation branches from right renal artery evidenced in the patient. Systemic administration of dexrazoxane could have presumably played a role either in skin manifestations outcome either in heart protection and reduction of hepatic and hematological effects of epirubicin.

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Una bambina di 1 anno e 7 mesi veniva condotta in Pronto Soccorso (PS) per comparsa di distress respiratorio improvviso con abbondanti secrezioni al cavo orale e successiva alterazione dello stato di coscienza. All'ingresso la bambina si presentava incosciente, con grave distress respiratorio e desaturazione (SpO2 80%), abbondati secrezioni alle vie aeree, bradicardia (80 battiti/min), miosi fissa. La bambina veniva sottoposta ad aspirazione e intubazione orotracheale. All'emogasanalisi veniva riscontrata una grave acidosi respiratoria. Mentre venivano effettuati ulteriori accertamenti (ematochimici, tossicologici e radiografia torace) veniva condotto in PS il fratello di 3 anni per difficoltà respiratoria ingravescente con abbondanti secrezioni al cavo orale. Il bambino si presentava cosciente, molto agitato con secrezioni abbondati al cavo orale e miosi fissa bilateralmente. Vista l'insufficienza respiratoria ingravescente il bambino veniva sedato ed intubato. All'approfondimento anamnestico la mamma riferiva che la sintomatologia era comparsa poco dopo l'applicazione al cuoio capelluto di un prodotto per pidocchi acquistato in Serbia. Veniva negata l'ingestione del prodotto o di altre sostanze potenzialmente tossiche. Veniva, pertanto, richiesta la consulenza del Centro Antiveleni di Pavia, per verificare l'esistenza di prodotti anti-pediculosi che potessero causare la sintomatologia presentata da entrambi i bambini (miosi, scialorrea, broncorrea e bradicardia). Veniva riferito che alcuni dei suddetti prodotti possono contenere organofosforici responsabili della sindrome colinergica. Nonostante non fosse possibile visionare il prodotto utilizzato, vista la severità del quadro clinico, veniva intrapresa terapia con atropina al dosaggio necessario per ottenere la scomparsa delle secrezioni. Portato in visione il prodotto utilizzato veniva confermato che si trattava di un prodotto antipediculosi ad uso veterinario contenente organofosforici. I bambini venivano trasferiti in Terapia Intensiva pediatrica dove presentavano un progressivo miglioramento delle condizioni generali, senza necessità di terapia con pralidossima. I bambini venivano estubati dopo 24 ore dall'accesso e dimessi il giorno successivo in benessere. I prodotti a base di organofosforici inibiscono in modo irreversibile le colinesterasi con conseguente accumulo di acetilcolina a livello della sinapsi che comporta sintomi muscarinici (sudorazione profusa, scialorrea, vomito, diarrea, bradicardia, miosi, broncorrea, edema polmonare acuto) o nicotinici (fascicolazioni, contratture muscolari, paralisi flaccida, tachicardia, ipertensione). A livello del sistema nervoso centrale è possibile osservare un quadro variabile dal rallentamento psicomotorio, fino a riduzione dello stato di coscienza, convulsioni, apnea, morte. I composti organofosforici sono principalmente utilizzati come erbicidi, pesticidi e insetticidi, ma sono contenuti anche in alcuni prodotti antipediculosi ad uso umano e veterinario. La mortalità da avvelenamento da organofosforici è alta ed è correlata alla dose, al ritardo diagnostico o ad una gestione impropria. Per la conferma diagnostica è utile il dosaggio delle acetilcolinesterasi eritrocitarie. La terapia dell'intossicazione grave da organofosforici si avvale di due antidoti: l'atropina che antagonizza gli effetti dell'acetilcolina a livello dei recettori muscarini-

ci e la pralidossima che è un riattivatore dell'acetilcolinesterasi.

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LUPINE INTOXICATION: A REMINISCENCE OF VERGA'S *I MALAVOGLIA**

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A 34-years old man comes to our Emergency Department (ED) reporting syncope with warning symptoms the previous night, after he stood up to drink a glass of water. He collapsed for unknown time and recovered spontaneously. He doesn't report previous health issues, allergies or drug intake. Clinical examination and ECG are normal. At standing, he complains about blurred vision and severe hypotension is assessed. Stool inspection is unremarkable for blood, laboratory red cell count only shows a mild anemia. Pupils are dilated. Cocaine, amphetamines and methamphetamines are not detectable in urine as well. Moreover, the patient reports dry mouth and failure to urinate, and eventually needs bladder catheterization. Lately, he tells us that he plays many sports and is a vegetarian. Suspecting an anti-cholinergic syndrome by unknown poisonous food, we contact the Poison Control Centre, whose operators suggest to investigate for a possible lupine intoxication. The patient actually confirms he has eaten a great amount of lupine soup in the past days. According to PCC suggestions, neostigmine 1 mg *i.v.*, activated charcoal 60 g and magnesium sulfate 30 g orally are given, and the patient is admitted for close observation. The following day, the patient is asymptomatic, orthostatic hypotension relapses, sight and urinating are normal and no arrhythmic events are pointed out. Anticholinergic syndrome is caused by several substances binding muscarinic receptors for acetylcholine (drugs - as antihistamines, antiparkinson and antidepressants, analgesics, antimuscarins, myorelaxants; plants - as Brugmansia arborea "Angel's Trumpet", Atropa Belladonna, Mandragora Officinarum, Datura Stramonium, etc). Typical signs and symptoms can be easily borne in mind through the doggerel "Hot as a Hare, Blind as a Bat, Dry as a Bone, Red as a Beet, Mad as a Hatter", which refers to hyperthermia, mydriasis, anhydrosis, hypotension, flushing, confusion and euphoria to seizures, ileus and urinary retention. Medical treatment requires life support, gastrointestinal decontamination with activated charcoal and magnesium salts purge, benzodiazepines for seizures, physostigmine 0.5-2 mg iv in 5 minutes: the dose can be repeated every 30-60 minutes, carefully monitoring hearth rhythm, watching for the onset of cholinergic symptoms (which are atropine-sensitive). Physostigmine is useful for unresponsive seizures, cardiac arrhythmias, hypotension, respiratory depression or coma. Lupines are vegetables mainly consumed as food in Southern Italy; we distinguish "sweet" varieties, which have an alkaloid content of approximately 130-150mg/kg, and "bitter" varieties, which need to undergo a de-bittering process through repeated hot-water washing to remove toxins before consumption (anyway, alkaloid content after de-bittering is approximately 500 mg/kg). Failure to remove alkaloids can result in poisoning. Lupine toxicity usually recovers in 24 hours with supportive therapy alone, but fatal cases have been reported, with a lethal dose of ca. 30 mg/kg bodyweigth. Physostigmine administration can successfully manage severe lupine intoxication not responding to supportive care.

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NORMOCYTIC NORMOCHROMIC ANEMIA AND ASYMPTOMATIC NEUTROPENIA IN A 40-DAY-OLD INFANT BREASTFED BY AN EPILEPTIC MOTHER TREATED WITH LAMOTRIGINE: INFANT'S ADVERSE DRUG REACTION

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Background: Epilepsy is one of the most common disorders that require continuous treatment during pregnancy. If lamotrigine is required by the mother, it is not necessarily a reason to avoid breastfeeding. In particular, maternal lamotrigine at low doses (lower than 200 mg die) is considered to be safe enough for the nursing infant. We describe a case of hematological adverse drug reaction an infant breastfed by a mother treated with low doses of lamotrigine. **Case report:** A 40-day-old, full-term, infant, came to our observation for inconsolable crying and recently ensued food refusal. At admission, pale skin, pale mucous membranes and a meteoric abdomen were evidenced in the infant. Infant medical history was uneventful: after at term, physiological delivery, he was fully breastfed with normal

postnatal development and adequate weight gain (birth weight: 3365 g, hospitalization weight: 4500 g). Mother's medical history was positive for epilepsy treated with lamotrigine: during pregnancy the drug daily dose was gradually increased from 120 mg to 200 mg in the third trimester; after delivery, lamotrigine was reduced to 150 mg. The mother also took folic acid throughout the pregnancy (400 mcg die), but she interrupted intake after delivery. At admission, infant blood tests highlighted normocytic normochromic anemia (hemoglobin 8.5 g/dL). Hemolysis, infections and bleeding were excluded; folic acid and vitamin B12 levels were normal. Lamotrigine-induced anemia was suspected: lamotrigine blood levels measured in the infant peripheral blood were 1.4 mg/L (therapeutic range in adults: 2.5 to 15 mg/L for most individuals). Breastfeeding was reduced, and the infant's diet was supplemented with milk formula. In spite of nursing baby's normal levels, folic acid (200 mcg die), iron (20 mg die) and vitamin B complex were started in both the infant and the mother. After 10 days, no anemia improvement was observed and an asymptomatic neutropenia (330 cells/mm2) appeared. At that point, breastfeeding was stopped and a rapid progressive normalization of the blood tests occurred. **Discussion:** Lamotrigine pharmacokinetics behavior changes over the course of pregnancy, at delivery, and during lactation. The lamotrigine clearance increases during pregnancy (maximum peak at delivery), decreases in puerperium and increases again to the initial values approximately at the third week post-partum[1], with subsequent variable infant exposure if maternal dose remains unchanged. Breastfed infants may undergo serious adverse effects, as observed in a 16-day-old infant that developed severe apnea and required resuscitation following exposure to lamotrigine through breastmilk (maternal dose 850 mg die, infant lamotrigine blood level 4.87 mg/L)[2]. Lamotrigine milk/plasma ratio is highly variable, as shown in the case series reported by Newport et al. The Authors estimated a mean milk/plasma ratio of 41.3% (range 33.0-49.6%), with infant plasma concentration corresponding to 18.3% of maternal plasma levels (theoretical infant lamotrigine dose: 0.51 mg/Kg/day; relative infant lamotrigine dose: 9.2%). At infant lamotrigine blood levels ranging from 0.6 to 1.8 mg/L, only mild thrombocytosis was observed [3]. In our case, normochromic anemia and neutropenia developed with lamotrigine blood concentration of 1.4 mg/L and improved only after breastfeeding discontinuation. Neonates are particularly at risk for high plasma levels due to the immaturity of their glucuronidation capability, required for drug clearance, and because plasma protein binding is relatively low[2]. If lamotrigine is required by the mother, it is not necessarily a reason to discontinue breastfeeding. However, breastfed infants should be carefully monitored for reported side effects (thrombocytosis, apnea, drowsiness or poor sucking, CNS depression), and for adverse drug reactions typically reported in adults treated with lamotrigine, such as rash or bone marrow depression. Measurement of lamotrigine serum levels should be suggested, in order to rule out toxicity if there is a concern.

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CLINICAL FEATURES OF SEVERE INTOXICATIONS ASSOCIATED WITH ANALYTICALLY CONFIRMED USE OF NBOME

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Objective: A novel class of synthetic hallucinogens called NBOMe emerged as new psychoactive substances (NPS) since 2009. NBOMe are N-2-methoxybenzyl analogues of the respective 2C-X substituted phenethylamines, and were first synthesized as 5-HT2A receptors activator at the Free University of Berlin in 2003[1]. We evaluate the prevalence and the clinical features of analytically confirmed intoxications by NBOMe over the last two years (2014-2015). **Case series:** Among the consecutive cases referred to our Poison Control Centre (as reference Centre in Italy) for suspected/confirmed poisoning by NPS between 2014 and 2015, 11 cases of NBOMe intoxication were evaluated (age ranging from 16 to 27 years-old; 82% males). Specific laboratory investigations (liquid chromatography-mass spectrometry) were performed in all cases on urine and/or blood specimens; 7 patients were positive for 25I-NBOMe, 2 for 25B-NBOMe, 1 for 25C-NBOMe and 1 for 25I- and 25H-NBOMe; patient's urine samples were also positive for 2C-I (7 cases), THC (7), amphetamines (3), MDMA (2) and ketamine (1 case). The patients declared assumption of LSD or another hallucinogenic substance (n= 6), mescaline (n=1), other or unknown substances of abuse (n=3), or no assumption. Three patients (27%) took part to a rave party. The most represented clinical manifestations were severe psychomotor agitation (91%), tachycardia (64%), seizures and rhabdomyolysis (45%), confusion (36%), hyperthermia (27%), coma, mydriasis, hallucinations and violent behavior (18% each); no lethal

cases were registered. Treatment consisted in sedation with benzodiazepines (6 cases), intubation and respiratory support (5 cases). Hospital stay ranged from 10 hours to 11 days for patients needed intensive care treatment. **Conclusions:** This case series confirms the presence of at least 4 types of NBOMe molecules (25I-, 25B-, 25C- and 25H-NBOMe) in the Italian territory. Seven patients were positive for 25I-NBOMe and 2C-I: this may be due to the metabolism of NBOMe to 2C analogues, or to the simultaneous abuse of 25I-NBOMe and 2C-I. Clinicians should be aware of the presence of this new psychoactive substances and their potential for toxicity, and they should suspect possible NBOMe assumption in patients reporting the recent use of LSD or other hallucinogens. All the cases have been reported to the National Early Warning System. **Acknowledgements:** Study carried out with the support of Antidrug Policy Department, Italian Presidency of the Council of Ministers.

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GESTIONE INFORMATIZZATA DELL'ARMADIO ANTIDOTI PRESSO IL PRONTO SOCCORSO PEDIATRICO REGINA MARGHERITA DI TORINO: PRIMI DATI RACCOLTI

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Background: Da Gennaio 2016 è in uso presso il Pronto Soccorso Pediatrico Regina Margherita un protocollo per garantire la necessaria dotazione antidotica, si è reso quindi necessario introdurre uno strumento per la gestione degli antidoti presenti in Pronto Soccorso, da qui l'idea di creare una interfaccia informatica per la gestione della giacenza antidoti. **Metodo:** Presentazione dello strumento informatico e studio descrittivo. Descrizione del nuovo metodo implementato presso la nostra struttura e dati preliminari sui casi di intossicazione accorsi da Gennaio 2016 a Giugno 2017 nei pazienti pediatrici (0-14 anni) giunti al nostro nosocomio. **Risultati:** Il programma informatico per la gestione del magazzino antidoti è stato un nuovo strumento a disposizione dell'equipe medico-infermieristica che si è dimostrato di semplice e efficace utilizzo. Sono stati registrati 268 casi di intossicazione, la fascia di età più esposta è quella 1-5 anni (68,66%) con incidenza superiore per il sesso maschile (59,2%) seguono i bambini tra i 5 e i 10 anni (9,7%), poi i lattanti sotto l'anno (9,3%), gli adolescenti tra i 10 e i 14 anni (8,96%) e oltre i 14 anni (3,3%). È l'ambiente domestico il luogo di maggiore rischio (84,3%) e i prodotti per l'igiene della casa le sostanze con cui più frequentemente avviene l'incidente (25,7%), seguito da farmaci assunti accidentalmente (22,8%) e i prodotti chimici (20,9%). Interessante è anche la percentuale di eventi dovuti a somministrazione accidentale di farmaci in sovraddosaggio da parte, principalmente, del caregiver: 10,8%. L'uso di antidoti è infrequente, solo il 16,7% degli event i ne hanno richiesto la somministrazione. Più ripetutamente si è trattato di carbone attivato (57,6%), seguito da N-acetilcisteina, simeticone, fomepizole, flumazelin e siero antivipera. **Conclusioni:** Al momento la fase di sviluppo del programma è terminata, la gestione è affidata ad alcuni componenti dell'equipe. I dati sono in fase di ulteriore elaborazione e riflettono, in buona parte, quello che è il panorama internazionale delle intossicazioni in ambiente pediatrico anche se con alcune differenze.

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NOSOCOMIAL TRANSMISSION OF *CLOSTRIDIUM BUTYRICUM* TYPE E RESPONSIBLE FOR TWO CASES (ONE OUTBREAK) OF INFANT BOTULISM

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Objective: Botulism may develop if a preformed toxin is ingested or if clostridia producing botulinum neurotoxins grows in the intestines or wounds, and toxin is released. Person-to-person transmission does not occur and poisoned patient not required isolation. We reported two cases (one outbreak) of nosocomial transmitted infant botulism (IB). **Case series:** Case 1: A 12-week-old infant (5 Kg bw) was admitted to the ICU because of feeding difficulties, weak cry, poor head control, mydriasis, generalized weakness, hypotonia, and acute/tympanic abdomen. The mother reported the presence of stypsis associated with abdominal colic (from 2 weeks) unsuccessfully treated with cimetropi-

um bromide. Due to the rapid neurological worsening with a floppy-baby hallmark, IB was suspected. Lab-tests confirmed type E botulism. Considering the serious conditions, the patient was intubated, treated with antitoxin and, subsequently, with clostridiocidal antibiotic (metronidazole) and PEG-4000 whole bowel irrigation by gavage. Clinical conditions progressively improved and the infant was transferred, 5 days after antitoxin administration, in the paediatric ward. Faeces resulted negative 12 days after antibiotic treatment. Case 2: An 8-week-old infant hospitalized from birth in the same ICU, presented a clinical picture of botulism 15 days after the case-1 admission. This baby was born at 26th weeks of gestation with a birth weight of 679 grams. During hospitalisation received supplemented human milk, D-vitamin, probiotics and caffeine. Laboratory investigation confirmed also for this patient type E botulism. The patient was intubated and supported in the respiratory function, and treated with antidote and antibiotic. Clinical conditions gradually improved with complete return to spontaneous respiration 7 days after antitoxin administration. He excreted C. butyricum type E from faeces for 15 days. Whole Genome Sequencing revealed that C. butyricum type E isolated from the specimens of the 2 patients were indistinguishable. No C. butyricum type E was detected in the ICU environmental samples collected after that the second case was confirmed by laboratory investigations. **Conclusions:** We report the first description of nosocomial transmission of C. butyricum type E responsible for two cases of IB: the two families and the two patients came from different geographical areas and never had any contact previously. Although isolation of these patients is not necessary, particular care should be taken to avoid nosocomial transmission of spores. The same procedures adopted to prevent nosocomial transmission of Clostridium difficile colitis could be successful implemented to reduce spreading of neurotoxins producing clostridia spores.

INSUFFICIENZA RENALE ACUTA DOVUTA A GASTROENTERITE IN PAZIENTE PEDIATRICO TRATTATO CON ENALAPRIL

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Background: La terapia con gli ACE inibitori può essere complicata da reazioni avverse come insufficienza renale acuta e ipotensione che possono comparire all'inizio della terapia oppure dopo un aumento del dosaggio. Ulteriori fattori di rischio includono ipovolemia o un contemporaneo eccessivo utilizzo di diuretici (Lappi et al., 2013). Riportiamo un caso clinico in cui tali effetti collaterali sono comparsi dopo anni di terapia in concomitanza temporale con una grave gastroenterite. **Case Report:** Paziente di 5 anni, 9 kg affetto da cardiopatia congenita, portatore di protesi mitralica e omozigosi DQ2 per la celiachia, è afferito al nostro pronto soccorso con grave ipotensione (PA 50/30 mmHg) e anuria. Era presente anemia importante (Hb 6.9 g/L, Ht 21.4%, MCHC 303 g/L). Dalla nascita era in terapia con enalapril 0.3 mg/kg/die, furosemide 0.9 mg/kg/die, idroclorotiazide 0.7 mg/kg/die e spironolattone 0.7 mg/kg/die. Cinque giorni prima dell'accesso in ospedale, è stata aggiunta terapia antibiotica con cefpodoxima 10 mg/kg/die per la comparsa di febbre e gastroenterite. Il paziente è stato ricoverato in terapia intensiva pediatrica, dove, nonostante il riempimento volemico l'ipotensione persisteva ed era presente insufficienza renale acuta (creatinina 4.5 mg/dl) e acidosi metabolica. A causa dell'ipotensione veniva iniziata infusione di noradrenalina 0.2 γ/kg/min e vasopressina 0.01 U/kg/h. Dopo 2 giorni, la pressione arteriosa si è normalizzata e l'insufficienza renale si è risolta con creatinina 0.2 mg/dl. Il decorso clinico è stato complicato da infezione polmonare da virus influenza A e il paziente è stato dimesso dopo 22 giorni di ricovero. Le concentrazioni ematiche di enalapril all'ingresso in terapia intensiva sono risultate di 10 ng/ml (range terapeutico 15-20 ng/ml). **Discussione:** In condizione di deplezione volemica, come nelle gravi gastroenteriti, il rene necessita alti livelli del angiotensina II per mantenere una adeguata filtrazione glomerulare per via della bassa pressione di perfusione. In tali casi, la presenza di Ace inibitori provoca una riduzione della velocità di filtrazione glomerulare dovuta a riduzione della vasocostrizione arteriolare efferente. Inoltre, i diuretici aumentando la natriuresi, aggravano il rischio di ipovolemia. Infine, è stato dimostrato che i pazienti pediatrici in terapia con ACE inibitori e con insufficienza renale, presentano rischio di ipotensione significativamente superiore rispetto ai pazienti con funzionalità renale nella norma (Ghazi et al., 2014). In conclusione, condizioni che incrementino il fabbisogno renale all'azione vasocotrittrice dell'angiotensina, come l'uso di diuretici e l'ipovolemia da gastroenterite del nostro caso, possono far aumentare la suscettibilità alle complicanze degli ACE inibitori.

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METAL RELEASE FROM SPINAL ARTHRODESIS: TWO CASES WITH IMPLANT FAILURE AND LOCAL METAL RELEASE BUT SLIGHT ELEVATED SERUM LEVELS

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Background: Metal spinal implant may determine either local either systemic metal release. However the potential relation between local, systemic metal release and implant outcome are at present critical aspects in scientific literature involving spinal implant[1]. We report two cases that presented implant failure needing surgical revision associated to local metal release and slightly elevated metal serum levels. **Case 1:** A 58-year-old male patient was referred to the Pope John XXIII Hospital ED after falling while working. X-ray of the thoracolumbar spine showed a complete L1 burst fracture. The patient underwent neurosurgical decompression, spinal stabilization and fusion of D11-L3 with USS-Low-Profile-system (DePuy-Synthes). After six months the patient report a sudden increase of the dorso-lumbar pain. A CT scan showed a dislocation of the caudal screws of the implant, on L2 and L3 vertebral body, with peripheral bone reabsorption. The patient underwent to vertebral implant removal, and L1, L2, L3 vertebroplasty. Intraoperatively a scar-like tissue with metallic pigmentation around the dislocated screws were present. Toxicological analysis evidenced blood metal concentrations as follows: aluminum 6 mcg/L (RV 1-6), titanium 5 mcg/L, tantalium 0.08 mcg/L (RV <0.1), niobium 0.1 mcg/L. After six months an RMI scans confirmed the vertebral stability of the lumbar segment; the patient report occasionally lumbar pain 10 of pain score. **Case 2:** A 41-year-old female patient was referred to the Neurosurgical Department with cervical pain, 70 pain score and serious dehiscence from an occipital decubitus lesion. The patient 10 years before at another hospital underwent a surgical cranio-vertebral stabilization and fusion for atlo-axial instability in rheumatoid arthritis. A cranio-vertebral implant removal and occipital skin plastic was performed. The implant removed was an Oasys occipito-cervical-system (Striker). Intraoperatively scar-like tissue with metallic pigmentation around the dislocated screws was sampled. The histopathhological analysis revealed fragments of fibrous tissue and sinovial tissue with a faint fibrosis, mild phlogosis and diffuse deposition of pigmented material. Toxicological analysis evidenced blood metal concentrations: chromium 1 mcg/L (RV 0.1-0.2), cobalt 0.3 mcg/L (RV 0.05-0.3), molybdenum 2.6 mcg/L (RV 0.2-1), titanium 12 mcg/L. After one month the patient report occasionally cranio-vertebral pain, 10 of pain score. Plain radiographic scans showed stability of the vertebral segment. **Discussion:** Metal spinal implant may be involved in several complication regarding implant corrosion, local metal release and systemic blood metal concentrations increase. In our patients implant failure and corrosion with local metal release at histopathology were presented; however only slightly elevated metal serum levels were evidenced. Systemic metal release from failed spinal implant may result in low serum concentrations if compared with the best described literature of metal-on-metal hip implanted patients that presented implant failure and local metallosis needing surgical revision. Our experience, also if limited, suggests that spinal implant bad-functioning, local metal release and initial inflammatory local tissue reactions could be undetected or underestimated by serum metal measurement. Serum metal monitoring may not always work as surrogate 'marker' for implant functioning, development of inflammatory local reactions or spinal metallosis.

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AN EXAMPLE OF A NEW TOXICOLOGICAL DISEASE AND A NEW SOCIAL PROBLEM RELATED TO THE ABUSE AND THE ADDICTION TO THE NEW PSYCHOACTIVE SUBSTANCES

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Objective: Because of incoming of New Psychoactive Substances (NPSs) tsunami wave, a changing on abusers represent a new challenge and a new disease. Due to the difficulty in diagnosis and in clinical management, NPS-abusers forces the clinicians to search the better way to manage poisoned patients. To manage acute intoxication, potential addiction and possible long-term sequelae - it's increasingly evident - a multidisciplinary approach is mandatory. Particularly, NPS-induced psychoses are frequently treated as an organic psychosis, but this is associated to therapeutic failure. We describe a case of a "human-tester" of different NPSs presenting with severe acute toxic effects and long-term psychiatric consequences. **Case report:** A clinical course of a 27 years-old male (chemist) with positive history of cannabis, MDMA and ketamine abuse is described. During 4 years (2012-2016) the patient was hospitalized (ICUs and/or psychiatric wards) 7 times for severe acute intoxication due to NPSs abuse. NPSs were carefully chosen for the dissociative effects and were purchased on internet. The length of stay of each hospitalization varied from 4 days

to 11 weeks. For severe conditions, during an ICU stay, patient underwent renal depurative treatments for 3 weeks. The main clinical manifestation (during acute phase) were severe psychomotor agitation, aggressiveness, delirium, hallucinations and dissociative state. Psychosis was unsuccessfully treated with haloperidol, clotiapine, aripiprazole, valproic acid and promazine. NPSs detected in biological samples during the different hospitalizations resulted dextromethorphan, methoxamine (MXE), MXE-bromo-derivative, ethylketamine, ethylnorketamine, norketamine, deschloroketamine, phencyclidine, 3-OH-PCP, 3-MeO-PCP, methoxyphencyclidine, dyphylline, methylphenidate, methoxphenidine and 5F-ADB. Brain PET revealed a severe diffuse widespread metabolic deficit as a cerebral "age" of about a 70 years-old subject. At present, the addiction behavior is still "active" and psychosis is pharmacology-resistant. **Conclusions:** NPSs addicted patient bring to different problems compared to classic substances abuser. NPS-related psychosis shown peculiar clinical aspects, and seems to be less responsive to standardized pharmacological treatments. As future perspectives, a multidisciplinary collaboration is necessary in order to identify a way for an optimal and appropriate management. To better understand all the crucial aspects of these novel toxicological diseases, experimental and clinical research on acute and chronic toxicity of NPSs are needed.

SU DI UN CASO DI DIAGNOSI TARDIVA DI BOTULISMO

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La tossina botulinica, prodotta dal batterio *Clostridium botulinum*, è il veleno biologico più potente tra quelli attualmente conosciuti. La dose minima letale per l'uomo è di 1000 ng/kg per via orale e 10 ng/kg per via inalatoria (Jaeger, 2002). L'intossicazione acuta da tossina botulinica si esprime come una grave malattia neurologica, il botulismo, caratterizzata da paralisi flaccida e che interessa, oltre l'uomo, anche varie specie di animali superiori. Il quadro sintomatologico è quello di una classica paralisi bulbare (Diplopia, Disartria, Disfonia, Disfagia "le 4 D") accompagnata da secchezza delle fauci e visione sfocata. La diagnosi si basa su criteri clinici e sull'anamnesi, supportata dall'esame elettromiografico, ed è confermata da test di laboratorio che identificano la tossina e gli organismi tossigeni nei pazienti e negli alimenti. Il botulismo alimentare è dovuto all'ingestione di tossina preformata, contenuta in alimenti contaminati da clostridi produttori di tossine botuliniche per mancata applicazione di corrette misure igieniche nella preparazione e trasformazione degli alimenti. Ciò avviene nella maggior parte dei casi nella preparazione domestica di conserve vegetali, sottolio o in acqua, più raramente in quelle prodotte artigianalmente o dall'industria. In questo report presentiamo il caso clinico di un paziente giunto in II cura alla nostra osservazione con diagnosi di insufficienza respiratoria post operatoria da probabile sindrome di Guillain – Barré. La Sindrome di Guillain – Barré, così come altre malattie neurologiche caratterizzate da paralisi flaccida, pongono qualche problema di diagnostica differenziale rispetto al botulismo. Il paziente, di sesso maschile, dopo la diagnosi di botulismo, confermata, in accordo ai protocolli vigenti del nostro Ministero della Salute, dopo tracheotomia e weaning respiratorio è stato dimesso in neurologia dopo 21 giorni di degenza in Rainimazione. Appare evidente l'enorme e pericoloso ritardo con cui fu avanzato anche il solo sospetto clinico dell'intossicazione. Anche se fortunatamente risolto positivamente il paziente, questo caso mostra chiaramente come piccole disattenzioni, ritardi, o superficialità possono avere conseguenze molto gravi.

METHOTREXATE THERAPEUTIC ERROR IN NON-ONCOLOGY SETTING

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Background: Methotrexate (MTX) originate as antineoplastic drug, but, from several years, it is largely used also in autoimmune/rheumatic diseases for its antiphlogistic properties. Adverse reactions are described after therapeutic dose, especially in patients with risk factors (e.g. renal impairment, drug-drug interactions, predisposing genetic polymorphisms). Moreover, MTX spread in outpatients may increase also the possibility of therapeutic error. High risk of toxicity is related to overdose. **Objective:** To evaluate the characteristics of the cases of MTX overdose due to therapeutic error in non-oncology patients. **Methods:** All cases of MTX overdose due to therapeutic error in non-oncology patients referred to our Poison Control Centre were retrospectively evaluated in a 8-year (06/2007-06/2016) retrospective study. Data about patients, intoxication circumstances and clinical manifestations were analysed. **Results:** Thirtyfive cases were included (50% male), aged between 17 and 86 years. In 5 cases patients were nursing mothers (not in treatment) to which MTX was wrongly sold by pharmacist instead of methylergometrine. In the remaining 30 cases, it came to patients who assumed prescribed MTX for the first time in their life for an autoimmune/rheumatic disease. In 27 cases wrongly assumption of prescribed dose occurred, in 2 patients MTX was administrated by incorrect way, and in 1 case was administrated despite presence of severe renal failure. In all the 28 patients that underwent an assumption

error, the weekly prescribed dose (range: 2.5–12.5 mg/week) was daily assumed (=17.5-87.5 mg/week); this mistake was recognized after a period ranging from 2 to 21 days. Clinical manifestations were characterized by mucositis (14/35), myelosuppression (12/35), asthenia (6/35), acute renal failure (5/35), diarrhea (4/35), vomiting (4/35), headache (2/35), hepatitis (2/35). All patients were treated with calcium levofolinate and forced alkaline diuresis. N-acetylcisteine was administered in 2 patients with hepatitis, and growth-factors in one. MTX plasma levels were available for 6 patients, resulting within recommended therapeutic range. No lethal cases were registered. In the 5 nursing mothers breastfeeding was stopped for 4 days. **Conclusions:** Medication errors is a cause of MTX toxicity. Most assumption errors are due to misunderstanding of medical prescriptions. Clear indications, possibly with electronic systems and explication to the patients are necessary in order to avoid these errors and the consequent toxicity. MTX serum quantitative determination is useful during therapy and to administer the correct dose of antidote in acute overdoses, but is not a good predictor of outcome in chronic overdose, due to the pharmacokinetic characteristics of the drug.

ANTIDOTE TREATMENT IN VIPER ENVENOMATION IN ITALY: A COMPARISON BETWEEN TWO ANTIVENOMS DURING FOUR-YEAR EXPERIENCE

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Objective: EU marketed viper antivenoms differ for pharmaceutical characteristics, equine/ovine origin, viper spp. neutralizing activity, dosage and registered route of administration. In Italy, hospital availability of 5 different antivenoms influence their use. Aim of this study was to evaluate the clinical response in envenomed patient treated with the two antivenoms (Zagreb and Biomed) mainly used in the last 4 years. There are no differences for host animal and fragment type [F(ab')2]; regarding the specific activity, Zagreb is declared active against Vipera aspis, ammodytes, berus, labetina and xanthine, Biomed only against Vipera berus. **Methods:** All viper bitten patients treated with one of the two antivenoms (administered according to manufacturer recommended dose) from 2013-Sep2016 were retrospectively assessed for sex/age, site of bite, time elapsed between bite and ED admission/antivenom administration, antivenom administered and acute/delayed adverse effects (ADR). Grading-Severity-Score (GSS) was applied at admission, at antivenoms administrations, and after 6-hours. Improvement was defined as amelioration/no evolution of local effects and/or no appearance of systemic effects (including neurological symptoms). Patients were follow-upped until discharge. **Results:** Sixty-six patients (age 44.3±27.2 y-o; male 70%) were included; 16 were paediatric (1-15 y-o). Considering geographical distribution, Vipera aspis spp. was mainly involved. Upper and lower limbs were involved in 88% and 12% of cases, respectively. Average time between bite and admission was 4 hours (15min-23hours); an average of 9 hours (40min-26hours) elapsed between bite and antivenom administration in patients with GSS 2 or 3. Both antivenoms were administered intravenously: Zagreb in 31/66 (47%) and Biomed in 35/66 (53%) cases. Clinical improvement was registered in 94% (29/31) and 57% (20/35) of patients treated respectively with Zagreb and Biomed (p=0.0007). Considering two subgroups [≤15 (n =16) or >15 (n=50) years old], Zagreb increases the probability of clinical improvement in both with more evidence in paediatric group (Zagreb=85.71% vs Biomed=22.22%, OR=16, p=0.041). Acute adverse reactions occurred after Zagreb (3 cases; angioedema, pruritus, bradycardia) and Biomed administration (1 cases; vasovagal syncope). Serum sickness (3 weeks later) occurred in 1 case (Biomed). **Conclusions:** An apparent less efficacy seem to exist for Biomed, both considering all patients and the paediatric sub-group, but these results should be cautiously evaluated because of the small paediatric population. Intravenous administration is usually safe (even if off-label used for Biomed). It remains difficult to ascertain which species of viper is responsible of the envenomation, and Biomed performance is probably influenced by the activity only against V. berus.

GAMMA-HYDROXYBUTYRATE INTOXICATION IN ITALY RELATED TO A PHARMACEUTICAL PREPARATION

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In Italy, gamma-hydroxybutyrate (GHB) is used to control withdrawal symptoms in the treatment of alcohol dependence. It is available in 10 or 240 ml bottle of 17,5% solution. **Objective:** This study evaluates a case series of voluntary intoxication by GHB in the trade pharmaceutical formulation referred to Italian Emergency Departments (EDs) and our Poison Control Centre in order to identify the characteristics of this intoxication in our country. **Methods:** We performed a retrospective analysis of all cases of pharmaceutical-GHB intoxication referred to our Poison Control Center over a nine-year period (2007-2015). All cases of admission to EDs for a confirmed and voluntary GHB poisoning were evaluated, while accidental intoxications (*e.g.* therapeutic error) were excluded.

Characteristics of the poisoned patients and clinical features were evaluated. **Results:** Four hundred and sixty-six of the 539 cases of pharmaceutical-GHB intoxication met the inclusion criteria (M/F ratio 1,39), aged from 16 to 78 (median age 39,45+/-9). The average dose taken (known in 318/466 patients) was 76,62 ml (13,4 g; range 1,75-49 g); 26,1% of the patients were admitted to the EDs during the weekend. The 41% of patients (n. 191) ingested only pharmaceutical-GHB, while other agents were co-assumed in 275 cases (59%): among these, the main ones are sedative-hypnotics (30%), antidepressants (19%), ethanol (26%), methadone (5%), substances of abuse (8%) and other drugs for the treatment of alcohol abuse (7,6%). Severe neurological impairment (GCS <9) was present in 56,22% of all the cases (276/466), and in 36,3% of the pharmaceutical-GHB pure intoxications (121/191). Twenty-one patients (4,5%) needed endotracheal intubation and supported ventilation (4,1% in pure intoxication and 4,7% in mixed intoxications). **Conclusions:** Compared to the previously published studies on GHB intoxication, this case series shows some peculiarities such as (i) higher average of age, (ii) high percentage of co-assumption of medications and ethanol, (iii) lower percentage of excitatory symptoms and (iv) a homogeneous distribution of the cases during the week. The use of GHB in Italy for the treatment of alcoholism addiction should result in an easier availability for patients at risk of abuse and could explain the peculiarities of our case series.

CARBON MONOXIDE MODERATE AND SEVERE INTOXICATIONS RELATED TO WATERPIPE USE

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Background: Narghile (waterpipe, hookah) is a traditional method of tobacco use. In recent years, its use has increased worldwide, especially among young people. Compared to cigarettes, narghile smoking can result in a greater exposure to several volatile compounds, including carbon monoxide (CO)[1]. We evaluate the waterpipe-related CO-poisoning to assess the severity of the intoxication. **Methods:** All cases referred to our Poison Control Centre in a height-year-period (April 2008-April 2016) for CO intoxication were retrospectively reviewed, and narghile-related cases were selected and evaluated for (i) patient data, (ii) clinical manifestations, (iii) carboxyhemoglobin (HbCO) level at admission, (iv) treatment and (v) outcome. **Results:** Sixteen patients (M/F 13/3), aged from 17 to 47, were identified as waterpipe-related CO poisoning. Height patients had smoked alone, while in the other eight cases the patients smoked with other people. 15/16 patients had smoked tobacco, while only one had smoked hashish. Ten patients referred to an emergency department because symptomatic: syncope (5/10), headache (7/10), dizziness (2/10), vomit (3/10), diarrhea (1/10), dyspnea (3/10). HbCO level of symptomatic patients at admission ranged from 5,3 to 23,2% (average 14,2+/-7). Six patients were asymptomatic and undergo medical evaluation just because they smoked together with symptomatic patients: nevertheless, their HbCO levels at admission were positive ranging from 5,6 to 18,3% (average 8,4+/-5). Five of six asymptomatic patients were discharged in twelve hours after cardiac evaluation and normobaric oxygen treatment. Eleven patients were hospitalized for further clinical evaluations and for normobaric (7/11) or hyperbaric oxygen treatment (4/11). All patients were discharged without sequelae. A forty-day clinical follow-up was performed. The symptomatic patient who smoked hashish manifested syncope with short pseudo paresis of limbs; his HbCO level was 11,5% three hours after smoking. **Conclusions:** Narghile smoking exposes to the same harmful substances of cigarette smoking (CO included), although in greater quantity due to the duration of smoking/inhalation (approximately 5 minutes for cigarettes, 50 for narghile) and to the combustion temperature. The amount of CO in smoke is mostly related to waterpipe size and tobacco type. Moreover, waterpipe smoker inhales CO as a result of the charcoal combustion. CO intoxication, even severe, may occur, and it's reasonable to believe that this cases are underestimated. This diagnosis should be considered in case of non-specific neurological symptoms.

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CASO CLINICO DI PRESUNTO LOXOSCELISMO

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Introduzione: Nel presente lavoro viene riportato un caso presunto di loxoscelismo, da morso di ragno violino (loxosceles rufescens), su una paziente di anni 71, giunta al PS dell'A.O.U. di Salerno, in compromesse condizioni generali. **Caso clinico:** La paziente di 71 anni giunge al PS dell'A.O.U. di Salerno intorno alle 22,00 per stato confusionale, ittero manifesto, vomito e SDA. I familiari riferiscono che la paziente ha assunto nei giorni precedenti pasti a base di funghi (non specificati). All'esame obiettivo si apprezza addome trattabile, diffusamente dolente, con esplorazione rettale negativa per sangue o melena. E' presente al terzo medio della regione laterale della coscia sinistra un bottone necrotico del diametro di circa 1 cm da cui si diramano strie linfangitiche centrifughe (fig. 1), con linfadenopa-

tia inguinale omolaterale. Tale reperto tenderà ad accentuarsi nei giorni seguenti (fig. 2), per poi iniziare progressivamente a ridursi dalla settima giornata (fig. 3), con tendenza a scomparire negli ulteriori giorni a seguire (fig. 4).

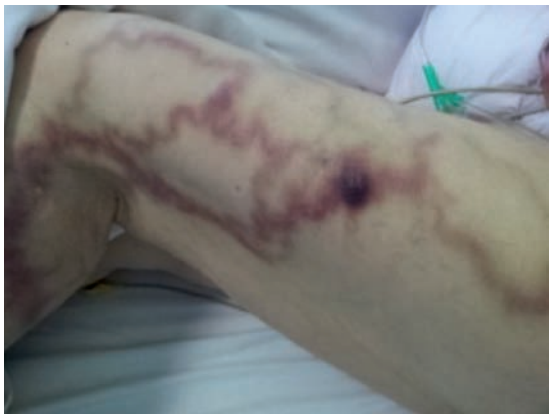

Figura 1.

La lesione si risolverà spontaneamente senza cicatrici. Gli esami di laboratorio di urgenza evidenziano una marcata anemia emolitica, con test di Coombs diretto ed indiretto positivo, dati di citolisi epatica e insufficienza renale acuta (precedenti esami nella norma), iperbilirubinemia, latticoacidosi, leucocitosi, rabdomiolisi.

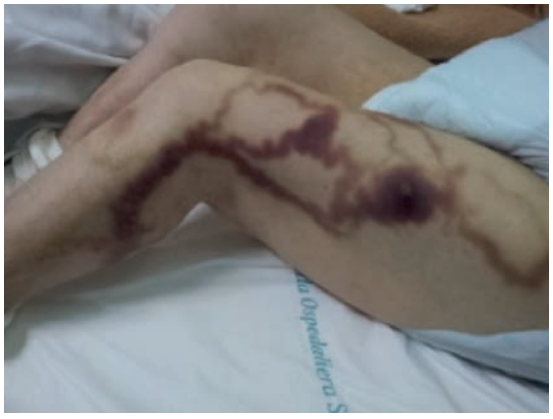

Figura 2.

All'ecografia addome reperto di epatosplenomegalia, senza dilatazione delle vie biliari intraepatiche e lieve dilatazione (7 mm) dell'epatocoledoco in paziente con colecisti ablata. ECG nei limiti. La paziente viene ricoverata in Medicina d'Urgenza, con prescrizione di terapia reidratante, cortisonica ed antibiotica e si praticano due prime emotrasfusioni (altre tre nei giorni seguenti). La mattina successiva si rileva torpore psichico, persistenza di ittero franco e dolorabilità diffusa dell'addome, apiressia. Si aggiunge in terapia nAC (300 mg/kg x 24 h), che verrà proseguito per ulteriori tre giorni, fino al miglioramento del quadro clinico. Oltre ai comuni esami di laboratorio, si effettua la ricerca dell'amanitina urinaria e dei markers epatitici (entrambi risultati negativi), prelievo per analisi citometrica (non evidenziate cellule indicative di processo linfoproliferativo) e per autoimmunità (ANA, AMA e ASMA assenti), Weil Felix (negativa), Toxoplasma, EBV, CMV (negativi). A partire dalla quarta giornata le condizioni cliniche della paziente evolvono in un progressivo miglioramento sia dal punto di vista clinico che laboratoristico. Sensorio integro, orientata. Addome trattabile, non dolente, alvo canalizzato a feci normocromiche, apiretica. Progressiva riduzione dell'ittero.

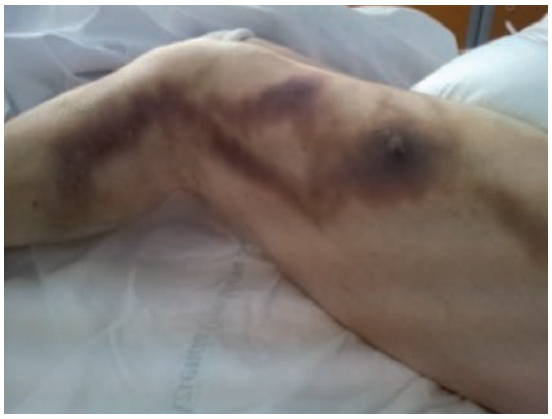

Figura 3.

Discussione: La più comune forma di aracnidismo in Italia, è rappresentata dal Loxoscelismo, conseguente al morso del ragno violino, loxosceles rufescens. L'affezione ha due forme principali di espressione: 1 - la localizzata, cutanea; 2 – la sistemica, viscerocutanea. La forma a localizzazione cutanea è costituita in genere da lesioni necrotiche, che talora possono anche essere drammatiche, tali da richiedere successiva chirurgia plastica. La forma sistemica è meno frequente e può essere caratterizzata da anemia emolitica, febbre e brividi, dolori articolari, vomito, ematuria, trombocitopenia, eruzione cutanea.

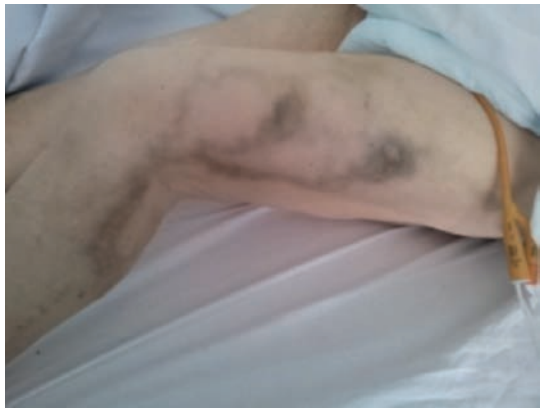

Figura 4.

Nei casi più severi, si possono manifestare disidratazione, massiva emolisi, CID, anuria, Insufficienza Renale Acuta, coma. La maggior parte di casi di loxoscelismo passano inosservati o non diagnosticati. Di solito il morso del ragno violino è indolore e il reperto dell'insetto è raro e casuale. La diagnosi etiologica è quasi sempre empirica ed ex adiuvantibus, basata sulla clinica e l'esclusione di altre possibili cause, pur essendo la lesione necrotica, più o meno marcata, patognomonica. Le più comuni sedi di morso si verificano ai glutei, alle cosce e ai piedi. **Conclusioni:** Nel caso riportato il ragno non è stato catturato e la diagnosi è stata basata sulle manifestazioni cliniche, cutanee e sistemiche, presentate dalla paziente, nonché dalla esclusione di altre malattie considerate nella diagnosi differenziale.

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