

Reye's-like syndrome in 13-year-old child (a case report)

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Key words:

Reye's syndrome, Reye's-like syndrome, coronavirus infections, antipyretics, paracetamol.

The article reviews the literature about classical and atypical Reye's syndrome, discusses the causes that contribute to its occurrence, provides criteria for diagnosis with the presentation of a Reye's-like syndrome case in the 13-year-old child. Reye's syndrome is a dangerous pathological condition characterized by acute encephalopathy and fatty degeneration of internal organs, mainly the liver.

There are different viral and bacterial infections that precede the development of Reye's syndrome, namely influenza, acute respiratory infections, chickenpox, entero- and rotavirus infections, whooping cough, mycoplasma infection, salmonellosis. For a treatment of these infections in the presence of fever, a number of drugs to lower the temperature, such as acetylsalicylic acid, ibuprofen, acetaminophen, diclofenac sodium is usually used.

Case presentation. We observed the case of a teenage girl with Reye's-like syndrome associated with coronavirus infection and antipyretic drug intake in the clinic.

Conclusions. Given the changes in the internal organs, namely the development of hepatic steatosis, therapy of such patients should be aimed at preventing fatty degeneration. In addition to classic Reye's syndrome, there is an atypical Reye's syndrome or Reye's-like syndrome, which mainly occurs in children under 5 years old with congenital disorders of fatty acid metabolism. Dosages of prescribing antipyretic drugs should be strictly based on the child's age and weight.

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синдром Рея, Рея-подібний синдром, коронавірусна інфекція, антипіретичні препарати, парацетамол.

Рея-подібний синдром у дитини віком 13 років (клінічний випадок)

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Наведено огляд фахової літератури щодо класичного та атипового синдрому Рея, розглянуто причини, що зумовлюють його виникнення, описано критерії встановлення діагнозу, представлено випадок Рея-подібного захворювання в дитини віком 13 років.

Синдром Рея – небезпечний патологічний стан, якому притаманні гостра енцефалопатія та жирова дистрофія внутрішніх органів, передусім печінки. Є низка вірусних і бактеріальних інфекцій, що передують розвитку синдрому Рея: грип, гострі респіраторні інфекції, вітряна віспа, ентеро- та ротавірусні інфекції, кашлюк, мікоплазмозна інфекція, сальмонельоз. Під час лікування цих інфекцій, коли є лихоманка, зазвичай використовують низку медикаментозних засобів для зниження температури: ацетилсаліцилову кислоту, ібупрофен, ацетамінофен, диклофенак натрію.

Презентація клінічного випадку. У клініці спостерігали випадок Рея-подібного захворювання в дівчинки підліткового віку на тлі коронавірусної інфекції та приймання антипіретичного препарату.

Висновки. Враховуючи зміни у внутрішніх органах, зокрема розвиток стеатозу печінки, терапію таких пацієнтів треба спрямовувати на запобігання жировій дистрофії. Крім класичного синдрому Рея, діагностують атиповий синдром Рея, або Рея-подібне захворювання, що виникає передусім у дітей віком до 5 років із уродженими порушеннями обміну жирних кислот. Призначаючи антипіретичні препарати, треба чітко дотримуватися дози згідно з віком і масою тіла дитини.

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Рея-подобный синдром у ребёнка 13 лет (клинический случай)

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Представлен обзор научной литературы касательно классического и атипичного синдрома Рея, рассмотрены причины, приводящие к его возникновению, приведены критерии постановки диагноза, представлен клинический случай Рея-подобного заболевания у ребёнка в возрасте 13 лет.

Синдром Рея – опасное патологическое состояние, которому присущи острая энцефалопатия и жировая дистрофия внутренних органов, преимущественно печени. Существует ряд вирусных и бактериальных инфекций, которые предшествуют развитию синдрома Рея: грипп, острые респираторные инфекции, ветряная оспа, энтеро- и ротавирусная инфекции, коклюш, микоплазменная инфекция, сальмонеллёз. В лечении этих инфекций при наличии лихорадки обычно используют ряд медикаментозных средств для снижения температуры: ацетилсалициловую кислоту, ибупрофен, ацетаминофен, диклофенак натрия.

Презентация клинического случая. В клинике наблюдали случай Рея-подобного заболевания у девочки подросткового возраста на фоне коронавирусной инфекции и приёма антипиретического препарата.

Выводы. Учитывая изменения во внутренних органах, особенно развитие стеатоза печени, терапия таких пациентов должна быть направлена на предупреждение жировой дистрофии. Кроме классического синдрома Рея, диагностируют

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атипичний синдром Рея, или Рея-подобное заболевание, которое возникает преимущественно у детей в возрасте до 5 лет с врожденными нарушениями обмена жирных кислот. При назначении антипиретических препаратов необходимо чётко придерживаться дозы согласно возрасту и массе тела ребенка.

Reye's syndrome is a pathological condition manifested by acute toxic encephalopathy in combination with fatty degeneration of internal organs, mainly the liver. This pathology was first described in 1963 by Australian pathologist R. Reye and co-authors, who observed about 21 cases of influenza in children who had taken acetylsalicylic acid (aspirin), whereupon 17 children had died [1]. The World Health Organization (WHO) experts recommend not to use acetylsalicylic acid for fever in children under 12 years. Refusal from acetylsalicylic acid in case of influenza and acute viral infections in the United States and the United Kingdom has significantly reduced the number of Reye's syndrome cases from 0.9 to 0.1 per 100000 children under 18 years old. It should be noted that acetaminophen (paracetamol) and non-steroidal anti-inflammatory drugs for antipyretic use are taken by many children, but Reye's syndrome or Reye's-like syndrome occurs among only a few of them, which probably indicates that this group of children may have latent mitochondrial dysfunction which can arise in case of taking antipyretic drugs for treatment of viral infection [1–3].

Reye's syndrome or Reye's-like syndrome, in addition to influenza, can occur on the background of other acute viral diseases, measles, rubella, chickenpox, entero- or rotavirus infections, rarely bacterial infections (mycoplasmas, chlamydiae, pertussis, salmonellosis, dysentery) [1,2,4].

In recent years, in addition to acetylsalicylic acid, the list of antipyretic drugs that may cause Reye's syndrome or Reye's-like syndrome has increased significantly: non-steroidal anti-inflammatory drugs, acetaminophen, diphenhydramine, mefenamic acid and valproic acid. Besides these drugs, the causes of these pathological conditions are insecticides, herbicides, some paints and solvents, hepatotoxic fungi [2,5].

The literature describes genetically determined cases of Reye's syndrome, the specified age when it occurs most often, namely – children from 4 to 12 years, less often – infants and over 18 years, but sex differences in the occurrence of this pathology are absent, that is, girls and boys are equally affected. Also, the seasonal variation of Reye's syndrome is described – from December to April, which is probably associated with an increased incidence of influenza and viral infections, as well as the possibility of recurrent course [4–6].

Diagnostic criteria for Reye's syndrome were formulated in 1990 by the Centers for Disease Control and Prevention (CDC), in particular:

- acute non-inflammatory encephalopathy (alteration in consciousness from confusion and drowsiness to coma, lumbar puncture – 8 leukocytes/ μ l, histological changes – signs of neuronal degeneration, cerebral edema without periventricular or meningeal inflammation);

- hepatopathy confirmed by either biopsy or autopsy is considered as characteristic of Reye's syndrome, specifically mild fatty degeneration of hepatocytes, significant steatosis, dystrophy, edema and swelling of mitochondria, absence of inflammatory cell infiltrates; or a 3-fold or greater increase in the serum levels of alanine aminotransferase

(ALT), aspartate aminotransferase (AST) (without jaundice) or ammonia. However, such patients have no other explanation for cerebral and hepatic disorders [1,2,5].

Later, in 2018, the criteria for Reye's syndrome were refined: a child under 16 years old with unexplained non-inflammatory encephalopathy combined with one or more symptoms: 3-fold or greater elevation in serum ALT and AST, or ammonia levels, or fatty liver disease. These criteria are also used for the differential diagnosis of Reye's-like syndrome [1,2,6].

Case report

Here is a case of our own observation of Reye's-like syndrome. A 13-year-old girl O., a resident of Ternopil, was admitted to the Intensive Care Department of Ternopil Regional Children's Clinical Hospital with a diagnosis of "suspected acute enteral drug poisoning". It was found from the patient history that symptoms had appeared suddenly with fever (temperature rise to 38.7 °C), nausea, repeated vomiting, which had brought no relief, myalgia, severe cephalgia, and restlessness. The child being home alone without parental supervision self-administered acetaminophen tablets containing 50 mg of the drug in each for 4 hours. According to the child, the frequency of taking the drug was 1 tablet per 30–60 minutes (the girl had taken 6–7 tablets for 2 hours), as headache, muscle pain and weakness were troubling her, and she tried to relieve the condition and eliminate these symptoms (neither the child nor her mother could not clearly state exactly how many pills had been taken). After that, the child fell asleep, her body temperature decreased to subfebrile levels within 2 hours of sleep, but the girl became inactive, sleepy, complained of progressive weakness, inadequately answered questions, then she developed confusion, that is why mother called the ambulance, and the child was admitted to Ternopil Regional Children's Clinical Hospital.

On admission, the child had impaired consciousness, confusion, drowsiness, general cerebral and meningeal signs were absent, she moved herself, but there was a loss of coordination, specific odor from the mouth or body was absent. The skin and visible mucous membranes were pale pink, no rash, the throat was without redness, submandibular lymph nodes were enlarged. In the lungs – vesicular breathing, no wheezing, RR – 18 per minute. Heart sounds were rhythmic, no murmurs, HR – 68 per minute, blood pressure – 110/65 mm Hg. The abdomen was symmetrical, soft, there was no muscle defense, the liver edge was 1 cm below the right costal margin, the spleen was not palpable. There were no abnormalities of urination or defecation. Blood oxygen saturation (SpO_2) was determined in the range of <96 %. SARS-CoV-2 RNA was established by PCR from nasal and oropharynx smears.

Data from additional examinations: complete blood count – lymphocytosis and insignificant leukopenia were observed (RBC $4.0 \times 10^{12}/l$, Hb 123 g/l, MCV 88 fl, WBC $3.6 \times 10^9/L$, bands 5 %, seg. 27 %, eos. 4 %, lymph. 61 %, mon. 3 %, ESR 2 mm/hr). Biochemical blood test – elevated transaminases, urea, increase in LDH (total bilirubin 12.5

mmol/L, total protein 76 g/L, ALT 428 IU/L (N <37 IU/L), AST 242 IU/L (N <39 IU/L), LDH 418 U/L (N 140–295 U/L), CPK 128 U/L, triglycerides 1.6 mmol/L (N <1.69 mmol/L), urea 12.1 mmol/L (N 2.5–8.3 mmol/L), creatinine 56 mmol/L. The clinical urine analysis revealed no pathology. Cerebrospinal fluid was not tested (the mother did not consent to it). On ultrasound of the abdominal cavity: the liver was moderately enlarged, the contour was clear, smooth, the structure of heterogeneous echogenicity, pancreas, spleen and kidneys – without changes. No pathology was detected according to coagulation test.

Blood group typing: O (I), Rh +. Stool test – without pathology. ECG: signs of metabolic disorders in the myocardium. Chest X-ray: enhancement of the pulmonary pattern on both sides, the contour of the heart without pathology. Examination by an ophthalmologist and a neurologist – no pathology was determined. EEG: data for the presence of local, diffuse or generalized epileptiform activity at the time of examination were not detected.

The child received a final clinical diagnosis of coronavirus infection, Reye's-like syndrome, toxic hepatitis. Taking into account that there is a concern about Reye's syndrome or Reye's-like syndrome in children under the age of 18 after taking acetaminophen and other antipyretic drugs, the child was diagnosed with Reye's-like syndrome in time and prescribed appropriate treatment. The child was assigned a comprehensive therapy aimed at correcting metabolic disorders, prevention of coagulopathy, and the development of cerebral edema (gastric lavage, cleansing enema, infusion therapy, hepato- and angioprotectors, glucocorticosteroids, anticoagulants, diuretics, vitamins D, C) in the intensive care unit. The girl's condition was with positive dynamics during the observation, and then she was followed up by a gastroenterologist in the somatic department.

Discussion

Most children with coronavirus infection do not have severe symptoms and need only symptomatic treatment, which includes antipyretic drugs. Fever is a common symptom of COVID-19, therefore, over-the-counter antipyretic drugs such as ibuprofen and acetaminophen are included in guidelines to relieve discomfort, reduce fever and enhance patient wellbeing. Despite the efficacy and tolerability of these drugs, an increase in side effects has been reported in recent years after their use in children [7–11].

There are classical (aspirin-induced) Reye's syndrome and atypical Reye's syndrome or Reye's-like syndrome, which has an identical clinical picture and the same etiological factors. It occurs mainly in children under the age of 5 with congenital disorders of fatty acid oxidation as a result of hereditary carnitine deficiency or Acyl-CoA dehydrogenase deficiency, metabolism of organic acids or amino acids, metabolism of urea, or with an organic lesion of the central nervous system (CNS) of another origin [12–16].

Classical Reye's syndrome is associated with generalized damage to mitochondria in the brain, liver, pancreas, kidneys, myocardium, muscles due to impaired oxidative phosphorylation and fatty acid oxidation processes with the formation of fatty degeneration. These damages are induced by intake of drug preparations containing acetylsalicylic acid or other salicylates [6,12].

According to the pathogenic mechanisms, pathomorphological damage of the CNS by toxic metabolites in Reye's syndrome are: damage to tissues and blood vessels of the nervous system, blockade of neurotransmitters, cerebral edema, demyelination, ischemic disorders, delayed brain development [12,13].

Reye's syndrome is characterized by severe liver and brain damage and usually begins with sudden nausea and vomiting, and vomiting is repeated and does not bring relief. Neurological disorders develop a few hours later, restlessness and emotional lability change to apathy and drowsiness. An altered level of consciousness rapidly progresses from lethargy to its loss and the development of cerebral coma. A child may be in a coma from one day to several weeks [1,6,12].

Clinical diagnosis of Reye's syndrome consists of several stages:

- 1) obtundation, lethargy, drowsiness, gait disturbance, slowed responses to stimulation, vomiting;
- 2) speech difficulties, the child stop moving and contacting with others, lack of appropriate response to stimuli, reflexes are preserved;
- 3) delirium, irritability, combativeness, disorientation, hyperreflexia, hyperventilation, foot clonus, the appearance of pathological reflexes, while respiratory movements and the reaction of the pupils to light are preserved;
- 4) coma, hypoventilation, lack of spontaneous breathing and the reaction of the pupils to light, decorticate rigidity (leg extension, adduction, and arm flexion), changing in muscle hypotonia, areflexia, seizures, flaccid paralysis, and respiratory arrest [2,8,15].

Changes in biochemical parameters due to aspirin or salicylates intake are quite convincing in Reye's syndrome, namely: an increase in the level of liver enzymes, urea and ammonia from 3 to 20 times of the norm with normal or slightly increased bilirubin levels. Significant hyperammonemia and elevated transaminases indicate the development of acute liver failure in such patients according to progressive necrosis of liver cells. A number of patients also have hypoglycemia, especially young children, electrolyte imbalance and blood clotting (prolongation of prothrombin time), increased levels of lactate dehydrogenase (LDH) and creatine phosphokinase (CPK) [1,2,8,15,16].

Morphological examination in Reye's syndrome reveals a picture of acute encephalopathy: cerebral edema, neurodegeneration, lipid vacuolization around small vessels, haemorrhages, and brainstem infarction. Electron microscopy detects neuronal damage, swelling of astrocytes and myelin sheaths. Autopsy reveals the enlarged liver and microvesicular accumulation of fat in hepatocytes. Massive steatosis, which is a characteristic histological pathognomonic sign of Reye's syndrome, occurs from the first hours of this condition. Mitochondria are damaged, deformed, edematous, and the formation of polymorphic cells is revealed. Lipid inclusions are found in the cytoplasm of renal proximal tubule cells, myocardium, pancreas; acute necrosis of pancreocytes may also develop [5,16,17].

The similarity of diagnostic criteria for typical (idiopathic) Reye's syndrome and atypical (Reye's-like syndrome), the occurrence of this pathology secondary to a viral infection, symptomatic treatment with paracetamol or other drugs of a similar action (ibuprofen, acetylsalicylic acid,

metamizole sodium) contributed to their unification into one group of heterogeneous diseases according to the similar mechanisms of origin [14,16,17–20].

In our opinion, Reye's-like syndrome diagnosis in the presented patient is unquestionable, since there were CDC criteria: acute non-inflammatory encephalopathy and hepatopathy with changes in ALT and AST, paracetamol intake for the viral infection in doses significantly exceeding the therapeutic doses for the age, multiple organ lesions with involvement of kidney (increased urea), myocardium (increased LDH, AST) and the absence of jaundice, lack of typical disease stage and rapid reversible positive development of clinical and laboratory manifestations [16,18–20].

The peculiarity of this clinical case is that it was developed in an adolescent, clinical symptoms progressed quite quickly (within a day). In presence of the condition, a 50 % solution of metamizole sodium was administered to the patient according to fever in the Intensive Care Department. It was concluded that the cause of the Reye's-like syndrome was not an infection, but the intake of certain medications in an inappropriate dose with underlying probable latent mitochondrial insufficiency.

Conclusions

1. The complexity of this clinical case is the symptomatic treatment. The main purpose of treatment for such patients is to restore the function of the liver and brain, as well as to prevent the development of irreversible complications.

2. Unfortunately, the mortality rate in children with Reye's syndrome is quite high, reaching 80–95 % depending on the brain damage, and it is less than 1 % in Reye's-like syndrome.

3. It is especially important to analyze such clinical cases now, during the coronavirus pandemic, since one of the symptoms in this viral infection is fever, and acetaminophen and ibuprofen, according to the guidelines, can be used to reduce body temperature in children of all ages.

4. Dosages of prescribing antipyretic drugs should be strictly based on the child's age and weight.

Prospects of further studies. The sooner Reye's syndrome (or Reye's-like syndrome) is diagnosed and the treatment is started, the more favourable is the prognosis for a child.

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References

- Koloskova, O. K., Tkachuk, R. V., Bilous, T. M., Kolyubakina, L. V., & Bogutska N. K. (2021). Kliniko-laboratorni osoblyvosti perebihu syndromu Reia v ditei: klinichniy vyppadok [Clinical and laboratory features of Reye's syndrome in children: a clinical case]. *Zdorovia dytyny*, 16(4), 309-316. <https://doi.org/10.22141/2224-0551.16.4.2021.237278> [in Ukrainian].
- Postnikov, S. S., Mikhailova, S. V., Bryusov, G. P., Kostyleva, M. N., Gratsianskaya, A. N., & Ermilin, A. E. (2018). Reya-podobnyy sindrom u rebenka 3 let [Reye-like syndrome in three-year-old child]. *Bezopasnost' i risk farmakoterapii*, 6(3), 103-110. <https://doi.org/10.30895/2312-7821-2018-6-3-103-110> [in Russian].
- de Bont, E., Bohnen, J., Verhoeven, R., Dinant, G. J., & Cals, J. (2020). Childhood fever: Parental paracetamol administration after consulting out-of-hours general practice. *European Journal of General Practice*, 26(1), 21-25. <https://doi.org/10.1080/13814788.2019.1676415>
- Chomomydz, I., Boyarchuk, O., & Chomomydz, A. (2017). Reye (Ray's) syndrome: a problem everyone should remember. *Georgian Medical News*, (11), 110-118.
- Weiner, D. L. (2018, April 02). *Reye Syndrome*. EMedicine. <https://emedicine.medscape.com/article/803683-overview>
- Royal College of Paediatrics and Child Health. (n.d.). *Reye-like syndromes*. RCPCH. <https://reyesyndrome.rcpch.ac.uk/reye-like-syndromes/>
- Venturini, E., Montagnani, C., Garazzino, S., Donà, D., Pierantoni, L., Lo Vecchio, A., Nicolini, G., Bianchini, S., Krzysztofiak, A., Galli, L., Villani, A., Castelli-Gattinara, G., & Italian SITIP-SIP SARS-Cov-2 pediatric infection study group. (2020). Treatment of children with COVID-19: position paper of the Italian Society of Pediatric Infectious Disease. *Italian Journal of Pediatrics*, 46(1), Article 139. <https://doi.org/10.1186/s13052-020-00900-w>
- Pessoa, F. S., Lacerda, E., Gonçalves, V. C., & Tanaka, B. N. (2021). Case Report: MIS-C Temporarily Associated With COVID-19 Complicated by Reye's Syndrome. *Frontiers in Pediatrics*, 9, Article 650697. <https://doi.org/10.3389/fped.2021.650697>
- Sammons, H. M., & Choonara, I. (2016). Learning Lessons from Adverse Drug Reactions in Children. *Children*, 3(1), Article 1. <https://doi.org/10.3390/children3010001>
- Bianconi, V., Violi, F., Fallarino, F., Pignatelli, P., Sahebkar, A., & Pirro, M. (2020). Is Acetylsalicylic Acid a Safe and Potentially Useful Choice for Adult Patients with COVID-19? *Drugs*, 80(14), 1383-1396. <https://doi.org/10.1007/s40265-020-01365-1>
- National Institute for Health and Care. (2020, May 01). *COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital*. NICE. <https://www.nice.org.uk/guidance/ng173>

- [12] Uppala, R., Dudiak, B., Beck, M. E., Bharathi, S. S., Zhang, Y., Stolz, D. B., & Goetzman, E. S. (2017). Aspirin increases mitochondrial fatty acid oxidation. *Biochemical and Biophysical Research Communications*, 482(2), 346-351. <https://doi.org/10.1016/j.bbrc.2016.11.066>
- [13] Mund, M. E., Gyo, C., Brüggmann, D., Quarcoo, D., & Groneberg, D. A. (2016). Acetylsalicylic acid as a potential pediatric health hazard: legislative aspects concerning accidental intoxications in the European Union. *Journal of Occupational Medicine and Toxicology*, 11, Article 32. <https://doi.org/10.1186/s12995-016-0118-5>
- [14] Rootring, E., Sargel, C. L., & Tobias, J. D. (2021). Acute Hepatic Dysfunction Related to Chronic Acetaminophen Administration. *The Journal of Pediatric Pharmacology and Therapeutics*, 26(5), 497-501. <https://doi.org/10.5863/1551-6776-26.5.497>
- [15] Weatherburn, C. J., Guthrie, B., Dreischulte, T., & Morales, D. R. (2020). Impact of medicines regulatory risk communications in the UK on prescribing and clinical outcomes: Systematic review, time series analysis and meta-analysis. *British Journal of Clinical Pharmacology*, 86(4), 698-710. <https://doi.org/10.1111/bcp.14104>
- [16] Ferretti, S., Gatto, A., Curatola, A., Pansini, V., Graglia, B., & Chiaretti, A. (2021). Atypical Reye syndrome: three cases of a problem that pediatricians should consider and remember. *Acta Biomedica*, 92(Suppl. 1), Article e2021110. <https://doi.org/10.23750/abm.v92iS1.10205>
- [17] McCrae, J. C., Morrison, E. E., MacIntyre, I. M., Dear, J. W., & Webb, D. J. (2018). Long-term adverse effects of paracetamol – a review. *British Journal of Clinical Pharmacology*, 84(10), 2218-2230. <https://doi.org/10.1111/bcp.13656>
- [18] Magrum, B. G., & Pickworth, K. K. (2020). Aspirin rechallenge in an adult patient previously diagnosed with Reye syndrome. *American Journal of Health-System Pharmacy*, 77(2), 123-127. <https://doi.org/10.1093/ajhp/zxz276>
- [19] Saragiotto, B. T., Machado, G. C., Ferreira, M. L., Pinheiro, M. B., Shaheed, C. A., & Maher, C. G. (2016). Paracetamol for low back pain. *Cochrane Database of Systematic Reviews*, 2016(6), Article CD012230. <https://doi.org/10.1002/14651858.CD012230>
- [20] Mund, M. E., Quarcoo, D., Gyo, C., Brüggmann, D., & Groneberg, D. A. (2015). Paracetamol as a toxic substance for children: aspects of legislation in selected countries. *Journal of Occupational Medicine and Toxicology*, 10, Article 43. <https://doi.org/10.1186/s12995-015-0084-3>