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Review Article

Hydrofluoric Acid: Burns and Systemic Toxicity, Protective Measures, Immediate and Hospital Medical Treatment

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Abbreviations: HFA - Hydrofluoric acid; OSHA - Occupational Safety and Health Administration (USA); AIHA - The American Industrial Hygiene Association; NIOSH - The National Institute for Occupational Safety and Health; ppm - parts per million; BSA - Body Surface Area; CaG - Calcium Gluconate; D5W - 5% Dextrose in water

Abstract

BACKGROUND: Hydrofluoric acid is a commonly used chemical in many industrial branches, but it can also be found as an ingredient in household products such as cleaning agents. Possessing high corrosive potential, HF acid causes burns and tissue necrosis, while when absorbed and distributed through the bloodstream, its extremely high toxic potential is expressed. Acute symptoms are often followed by pain, particularly in the case of skin burns, which intensiveness does not often correlate with the expressiveness of the clinical findings. Even exposure to low-concentrated solutions or gasses, or low-doses of high-concentrated acid, may provoke delayed systemic disorder which may eventually have a lethal outcome.

AIM: Therefore, having information regarding the possible hazardous effects of hydrofluoric acid usage, a variety of symptoms, as well as a treatment approach, is of great importance in the case of HF exposure.

METHODS: Available scientific articles published in literature databases, scientific reports and governmental recommendations from the internet websites, written in English, using the following search terms "Hydrofluoric acid, skin burns, eye injury, ingestion, inhalation, systemic toxicity, decontamination, antidote, medical treatment" have been reviewed.

RESULTS: This review is useful not only for physicians but for everyone who may come in contact with a person exposed to HF acid.

CONCLUSION: It highlights the mechanism of action, presents the acute and chronic symptoms, personal and general protective measures and devices that should be used, as well as decontamination procedures, immediate, antidote and hospital medical treatment.

Introduction

Hydrofluoric acid as a chemical compound with a high reactivity is used in many industrial branches: fluorine industry, glass industry, stevedoring and transportation industries, semiconductor industry, stainless steel and aluminum manufacturing, electronic components manufacturing, metal finishing and metal rust removal industry, inorganic and organic chemical manufacturing, mineral processing, petroleum refining, fire extinguishers manufacturing, as well as waste and disposable service sectors [1], [2], [3], [4], [5]. In the dental industry and every-day clinical practice, HF acid is used as an etchant agent for ceramic materials [6], [7], [8]. Hydrofluoric acid can be found in consumer products for marble, brick and stone cleaning, as a rust removal, in automobile wheel cleaners, toilet bowl cleaners, air conditioners cleaners, and as insecticides [9], [10], [11], [12], [13], [14].

Unintentional exposure to hydrofluoric acid or gases, with health consequences, may occur in case of inappropriate operation, inadequate protection, when having machine problems, explosion of HF containers and tanks, during the traffic accidents [1], and inattentive usage of household agents [10], while intentionally, in case of suicide [11], [12], [14] and murder. There are cases of intoxicated children when domestic cleaners, in appropriately stored, were accidentally ingested [13].

Dermal burns, eye injury and gastrointestinal or respiratory acute symptoms may be provoked when in direct skin/eye contact with HF acid, ingestion of the solutions or inhalation of fumes or HF vapours. Systemic intoxication including electrolytic misbalance, enzyme inhibition, cardiovascular, pulmonary, renal and neuromuscular symptoms happens when fluoride ions are absorbed into the bloodstream after dermal exposure and other mucous membranes, and distributed in all tissues and organs. Chronic symptoms may even occur several months after HF ingestion [12] or may persist with months after the long-time respiratory exposure [3]. Sometimes, systemic intoxication has a lethal outcome [15], [16], [17], [18], [19], [20].

The tissue damage and the degree of toxicity are determined by the acid concentration, the exposure time, the contaminated body surface area, the time elapsed between exposure and decontamination i.e. hospital care [21], [22], [23], and person's age as well [13], [24].

Decontamination, antidote therapy and hospital treatment, implemented promptly, are of great importance to prevent penetration of the hydrofluoric acid deep into the tissue, to disable dissemination of the fluoride ions through the bloodstream, or to minimise the progression of organs' damage.

The purpose of this review is to present the properties of a hydrofluoric acid, its corrosiveness, toxicity and mechanism of action, acute and chronic symptoms after the HF exposure, describes preventive and protective measures, as well as procedures for decontamination and HF neutralisation, antidote and hospital medical treatment.

HF Acid Properties

Hydrogen fluoride (HF) has several synonyms: Hydrofluoric acid, Fluoric acid, Hydrofluoride, Fluorine monohydride, Fluorane.

Physical properties: As a gas, HF is a diatomic compound of hydrogen and fluorine atoms, while as a liquid, it is a polymeric compound with strong hydrogen bonds between the chains [8]. Both, anhydrous hydrofluoric acid and aqueous solutions are colourless, fuming gas or liquid with a strong, irritating odour. Its disagreeable, pungent odour, even at the concentration of 0.04 ppm (which is considerably less than the OSHA PEL - Permissible Exposure Limit of 3 ppm), is a warning sign of the presence of the potentially dangerous substance. It readily dissolves in water forming a colourless hydrofluoric acid solution that when diluted (exothermal reaction) is visibly indistinguishable from water [4], [24], [25], [26].

Some of the physical properties of the Hydrofluoric acid are presented in Table 1.

Table 1: Physical properties of the hydrofluoric acid

Molecular Formula:	HF
Molecular Weight:	20.006 g/mol
Boiling point:	20 °C (68°F) at 760 mm Hg
Freezing Point:	-83 °C (-117.4 °F)
Specific gravity:	0.99 at -7 °C (19,4 °F); 1 for liquid at 20 °C (68 °F) (water = 1)
Density:	1.002 at 0 °C / 4 °C
Vapour pressure:	783 mm Hg at 20 °C (68 °F); 400 mmHg at 2.5 °C (36.5 °F)
Vapour density:	1.27 at 34 °C (air=1)
Surface Tension:	10.2 mN/m at 0 °C
pKa:*	3.15
The heat of Vaporization:	7.493 KJ/mol at 101.3 KPa
Solubility:	Miscible with water, very soluble in alcohol, soluble in many organic solvents
Flammability:	Nonflammable, explosive or oxidising

*acid dissociation constant

Chemical properties: Hydrofluoric acid is characterised by high reactivity - it reacts with metals, glass, concrete, enamels, pottery, rubber, leather and many organic compounds [24], [25], [26]. Consequently, it is commonly used in many industrial sectors and as a domestic cleaning agent. HF has a unique ability to react with many silicon compounds, including glass [9], thus commonly used as an etchant agent in the glass industry and before adhesive luting of ceramic restorations in dentistry [27].

Preventive Measures when Working with Hydrofluoric Acid

Because of its high corrosiveness and toxicity, the extraordinary caution when using is recommended. Hydrofluoric acid should be exclusively used inappropriately equipped industrial sectors and laboratories, must not be applied on the restorations in the oral cavity (when used in dentistry), while attending, when using household and cleaning agents, is recommended. The last one should be stored out of reach of children. Personal and general protective equipment and measures should be implemented.

The person who uses HF acid should be aware of the toxicity of this agent and be familiar with all information and procedures regarding the safety when using, way of transporting and storing the acid, managing with HF containing waste, decontamination

procedures, antidote and medicaments that should be used in case of contact and intoxication [4], [5], [24], [25], [26], [27]. Protective equipment and measures, as well as managing with HF containing waste and spills are presented in Table2.

Table 2: Personal and general protective equipment and measures, medicaments used in the first aid kit, and managing HF containing waste and acid spills

Personal Protective Equipment when working with/using HFA	***General Protective Equipment*** at the working/laboratory place
Laboratory coat	Handled inside of a fume hood
Long pants	Ventilation/exhaust system
Acid resistant apron	Sign "Danger, Hydrofluoric Acid Used in this Area."
Close-toed shoes	Easy access to a good supply of running water
Tightly sealed goggles	Safety shower and eyewash
Full-face shield in conjunction with goggles	The Standard Operating Procedure (SOP) document
Rubber gloves: nitrile, butyl or neoprene	
Respiratory filter device	
Protective Measures HFA containers	***First aid kit*** medicaments
Polyethylene or Teflon	2.5% calcium gluconate gel
Clearly labelled	1% calcium gluconate eyewash
Securely supported and not likely to tip over	a solution of 0.13% benzalkonium chloride
Tightly closed and kept in a safe place	
Away from heat and direct sunlight	
Managing HF Containing Waste	***Managing HF Acid Spills***
Neutralisation of the solution using powder: Na_2CO_3, Ca_2CO_3	HF-specific absorbents Aqueous $Ca(OH)_2$ or $Mg(OH)_2$
Neutralised diluted solution should be disposed under running water	The neutralisation should be performed slowly to avoid an exothermic reaction that will speed up the evaporation of the HF and increase the risk of exposure and intoxication
Chemically resistant container, clearly labelled with a "Hazardous Waste" tag	

Corrosiveness and Toxicity

Hydrofluoric acid is characterised by its corrosiveness and high local and systemic toxicity. At room temperature (20°C), it has a strong acidic pH-value of 2.0 [27]. However, the devastating effects are not based on the low pH value, but on the toxicity of this acid [9], [21], [22].

Routes of exposure: There are three different pathways through which HF acid could be absorbed into the human body - skin/eye contact, inhalation and ingestion. The most frequent exposure is by cutaneous contact with the aqueous solution, no matter if the skin is intact or damaged [28], [29], [30], [31], [32]; it could also be absorbed through eyes [33], [34]. Inhalation intoxication occurs not only from exposure to hydrogen fluoride gas [17], [35], but also from vapors arising from concentrated hydrogen fluoride liquid [20], [36], while ingestion [14], [37], [11] of even a small amount of this acid is likely to produce systemic effects and may be fatal [13], [16], [18], [38], [39].

Mechanism of action: Easy penetration through the skin, soft tissues and lipid membranes are enabled by low charging of undissociated hydro fluoride molecules. Once in the tissue, the HF molecules dissociate in hydrogen cations and fluoride anions [9].

There are two primary mechanisms through which HF acid causes tissue destruction. The first occurs due to the activity of corrosive hydrogen ion when using a high concentration of this acid (>50%) and is associated with cutaneous and ocular lesions, as well as digestive and respiratory mucous membrane damage. Corrosive burns are similar to those provoked by other acids: they occur immediately, with visible tissue destruction, grey areas, ulceration or necrosis, followed by intense pain [9].

The latter is caused by cytotoxic fluoride anion responsible for local and systemic toxicity when HF acid products with high, as well as with low concentrations have been used [23], [40]. The fluoride ion is very small and diffuses readily in the aqueous media [9]. Absorbed into the bloodstream, it is carried to all body organs in proportion to their vascularity and fluoride concentration in the blood [16], [41]. When reacting with cellular calcium and magnesium, forms insoluble chelates, CaF_2 and MgF_2, thus provoking local calcium depletion and inhibition of Na^+K^+ ATP-ase pump. Subsequently, the cell membrane's permeability to potassium is increased resulting in local hyperkalemia. High lipid affinity induces liquefaction necrosis and cellular death, thus destructing the nerve and blood vessels, tendons, bone structures and all other tissues [23],[42]. These effects are due to the presence of fluoride ion and differ from other acids, in which the feature of the free hydrogen cations to provoke coagulative necrosis, which retards the further penetration into the tissues, is expressed [9], [11].

Fluoride Distribution: Deposition of the fluoride in the different tissues is characteristic: as the fluoride is excreted through the urine, after an acute exposure to fluoride-containing solutions, the most of the fluoride is deposited in the kidney, then in the liver and the spleen; insignificant amount has been detected in the bones [16]. Rapid excretion and removal of the fluoride from the kidney occur within 24 hours [43]. However, after chronic exposes, a large amount (about half of the dose) is deposited in the bones, while the kidney serves as a temporary depositing organ.

Referential exposure limits: Systemic effects are potentially lethal, depending on the acid concentration and available amount of free fluoride ions [44]. Referential exposure limits and HF burns with a high risk to develop lethal electrolyte imbalances are presented in Table 3 [4], [24].

Special attention should be paid if intoxicated persons are children [13]. Because of their relatively larger surface area: body weight ratio, children are more vulnerable to the hydrofluoric acid absorbed through the skin. When exposed to its evaporations, larger doses are inhaled because of greater lung surface area: body weight ratio and increased minute ventilation per kg weight compared to adults. Additionally, vulnerability to corrosive agents is greater because of the relatively smaller diameter of

their airways [5], [24], [25].

Table 3: Exposure limits and HF burns that occupy various BSA depending on the acid concentrations that could have a lethal outcome

Exposure limits	**3 ppm**[*] - maximum concentration of a chemical substance that an employee may be exposed to over an 8-hour work shift; eyes and throat irritation, if not protected, have been noted. **20 ppm**[**] - maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing or developing irreversible or other serious health effects or symptoms, which could impair an individual's ability to leave the contaminated area, and take protective action. **30 ppm**[***] - immediately dangerous to health or life concentration.
HF burns with a high risk to develop lethal electrolyte imbalances	1% BSA burn with anhydrous HF 5% BSA burn with >70% concentrated HF 7% BSA burn with 50–70% concentrated HF 10% BSA burn with 20–50% concentrated HF 20% BSA burn with <20% concentrated HF Prolonged exposure or long delay for treatment in minor HF burns Ingestion of HF at concentrations >5% Inhalation of HF at concentrations >5%

allowed by OSHA[*]; according to AIHA[**]; established by NIOSH[***]*1%, BSA is an area equal to a hand palm.

Symptoms

Dermal exposure: Skin burns

A 10-year [1], a 11-year [20], a 15-year [30], a 20-year [2] and a 22-year [29] retrospective epidemiological studies revealed that chemical burns encountered in a Burn centres caused by hydrofluoric acid are one with the most frequent occurrence, especially in the regions with highly developed industry. The most common sites of injury are the head and neck, hands, legs and arms [1], [45]. HF burns might be accompanied by ocular injuries, respiratory and digestive tract disorders [1].

Transdermal penetration of the fluoride ions depends on the exposure time and HF acid concentration, while intradermal accumulation is dose-dependently. Fluoride penetration increases four-times by extending the exposure time from 1 to 3 min (with no further increase when the exposure is prolonged to 10 min) and is exponentially increased with increasing the HF concentration from 5% up to 50%. Also, intradermal pH decreases with increasing the HF concentration and exposure time [46]. Accordingly, epidermal alterations can be detected after 3 min exposure to only 5% HF. Severe damage including coagulation necrosis of deeper dermal layers is provoked by HF concentration of ≥ 30%, with a considerable intradermal accumulation of 13-67% of total absorbed fluoride [47]. When exposed to 70% HF for only 20 sec, cellular alteration in four to five epidermal layers is noted by 1 min after the exposure. Within 5 min, HF acid completely penetrates to the human dermis [44], [48]. Coagulation necrosis including acidophilic cellular cytoplasm and pyknotic nuclei in all skin layers have been detected 1 h after exposure, while complete necrosis of the epidermis and disintegration of the structures have been observed by 24 hours [49].

Further penetration of the fluoride ion through all epidermal and dermal layers into the subcutaneous tissue, causes ulceration and severe destruction such as complete loss of the soft tissues on the place of contact, including myolysis, tenosynovitis, decalcification and osteolysis [4], [9], [32], [50].

Skin damage symptoms are directly related to the acid concentration. Strong concentrations of more than 50% HF acid cause immediate, severe, throbbing pain and a whitish discolouration of the skin [51], vesicle surrounded by an erythematous flare [52], which eventually transforms into the blisters containing necrotic tissue. Reduced motor activity, decreased sensitivity and ischemia provoked by arterial vasospasm might be additional symptoms in fingers' burns [53]. Necrotic dermal tissue detached from the subcutaneous tissue has been observed in third-degree skin burns provoked by 50% HF acid [19].

An autopsy finding of a man who died from a cardiopulmonary arrest 30 min after the exposure to 60% HF acid, with the skin burns that occupy 30% of the TBSA, revealed greenish-gray or black coloring skin with thin circumferential erythema and severe liquefaction necrosis, with completely lost elastic fibers within the dermis, and severely affected wall of large vessels within the subcutaneous layers. Immediate penetration of the fluoride ions into the deep layer of the skin and their rapid dissemination through the bloodstream resulted in the development of acute systemic toxicity with the lethal outcome [15].

Dilute solutions from 20% to 50% may provoke pain and swelling, with erythema and vesicles formation on the contact area, which may be delayed up to 8 hours [21].

Acid solutions with concentration lower than 20% may cause serious injury (deep burns and tissue necrosis) 12 to 24 hours or several days after the exposure, without immediate pain [9], [22], [23], [32], [42], [54].

The severe pain, that is the first symptom of an intensive HF burns, results from the neuronal depolarization, disruption in neuronal conductivity and nerve ending irritation provoked by hyperkalemia in extracellular spaces, a compensatory mechanism for reduced levels of calcium ions which have been bound by the fluoride [23], [28], [40]. In case of burns provoked by low-concentrated HF acid, the onset of pain is a result of the long lag time in pH drop [46].

Ocular exposure: Eye burns

Irritation and immediate severe pain, followed by lacrimation are first signs after eye exposure. Conjunctivitis followed by oedema and congestion [45], oedema of other structures of the eye, mydriasis, nystagmus, and corneal erosion and ulceration, with corneal opacification and non-visible iris as

complications, may result from even minor hydrofluoric acid splashes [33], [55]. Prolonged HF exposure can lead to loss of vision and total eye destruction. Ocular burn with a complete diffusion into the cornea has been detected within 4 min exposure to 2.5% HF acid [48].

Gastrointestinal exposure

Ingestion of a solution of hydrofluoric acid [13], [14], [37], [38], causes strong caustic effect on the mouth and throat, erythema, ulcerations and bleeding of the oral mucosa, with the risk of perforation of the esophagus and/or stomach, erosive gastritis [16] followed by severe abdominal pain, dysphagia, nausea, vomiting and diarrhea, that eventually may progress to hemorrhagic gastritis, hematemesis and melena [11], [12], [39], [41]. Liver congestion, hepatocellular swelling and pancreatitis may also be present [16].

An autopsy finding of a person who accidentally ingested a mixture of hydrochloric and hydrofluoric acid revealed haemorrhages in the gastrointestinal tract, brownish discolouration of the oesophagal, gastric, duodenal and small intestinal mucous membranes with necrosis foci reaching the deeper layers of the walls, numerous ulcerations in the oesophagus and the stomach, and congested mucous membrane of the large intestine [18].

Respiratory exposure

Symptoms from respiratory system may occur when exposed to HF gas, fumes or vapours which arise when liquid acid evaporates on increased ambient temperature; in the case of a pulmonary aspiration while ingesting [1]; as a systemic toxicity symptom after HF acid ingestion [16], [18]; as a respiratory complication after HF splashes on the skin [24], or after severe dermal burns [45].

The toxicological effect of HF gases or vapours on the airway epithelia depends on the inhaled doses: when exposed up to 1.5 mM HF, no toxic effect has been observed; repairable damage to the epithelial cells has been detected when inhaled 7.5 mM HF, while severe, irreversible damage has been caused by 75 mM inhaled HF gas [48].

Inhalation of toxic gases or vapours provokes nasal irritation and inflammation, dryness and mucosal bleeding with subsequent ulceration and/or perforation of nasal septum, erythema and oedema of the oral, nasal end laryngeal mucous membrane. Continued exposure can results in coughing, dyspnea, laryngitis, laryngospasm and retrosternal pain, followed by chills, fever, and cyanosis [5], [56]; it has a devastating effect on the trachea and bronchi causing tracheobronchitis, bronchiolar obstruction [10] and bleeding accompanied by stridor and wheezing. Gaseous HF when reaches the pulmonary tissue provokes pulmonary oedema and congestion, pleural effusion, pneumonia [16], [57], and even partial or complete lung collapse [9], [40]. Chest radiograph revealed pulmonary oedema [57] or diffuse infiltrative shadows over the lungs' parenchyma [35], [56]. Acute respiratory failure may even lead to a lethal outcome [20] with little to no additional signs of trauma [17]. Chronic, repeated exposure to hydrofluoric acid-containing fumes may provoke pulmonary alveolar proteinosis followed by long-lasting dyspnea [3].

The presence of pale bronchial mucus on the bronchial membrane and congested, edematous mucosa several days after skin exposure have been confirmed by fiberoptic bronchoscopy [45]. Extravasations and hemorrhagic infarcts have been detected in the lungs after fatal accidental ingestion of a mixture of hydrochloric and hydrofluoric acid [18].

Systemic poisoning

Absorption of the fluoride ions into the bloodstream after dermal HF exposure, ingestion, or inhalation, and their distribution in all cells [16] may result in systemic toxicity [28]. The degree of toxicity and the outcome depends on the HF concentration and duration of exposure, burn surface area and burn depth, and the time elapsed between exposure and decontamination/medical treatment [15], [45].

When exposed to diluted solutions or low-saturated gas, the symptoms are often delayed. Even a severe dermal burns provoked by concentrated HF acid with symptoms of systemic poisoning, when treated in timely manner with appropriate therapy, may have favorable outcome, as in the following cases: face and neck exposure to 100% HFA [56], [57], skin burns provoked by 71% HFA occupying 7%TBSA [58], skin burns provoked by 70% HFA occupying 10%TBSA [59], face and neck exposure to 53% HFA [60].

Cases with expressed systemic disorder including electrolyte imbalance, enzyme inhibition, symptoms of hypovolemic shock, multiorgan failure, acute respiratory failure and numerous ventricular fibrillation or asystole, in which resuscitation procedures have been ineffective, have a lethal outcome [15], [18], [19].

Laboratory findings

Due to the high affinity of fluoride ion towards calcium and magnesium, and formation of insoluble salts, massive systemic electrolyte imbalance, which is difficult to counterbalance, may occur [53], [60]. This includes hypocalcemia, hypomagnesemia [45], hyperkalemia [14], [15], [19] or hypokalemia [2], [61], [62], fluorosis and metabolic acidosis [1], [19]. Enzyme inhibition and coagulation disorders [15], [22] are common findings as well.

Cardiovascular system disorder

The electrolytic imbalance affects the cardiovascular system, provoking hypotension and vasospasm [53], [63]. Hypocalcemia causes decreased myocardial contractility and intermittent prolongation of the Q-T interval, which is associated with degenerative rhythms such as torsades de pointes, a specific type of ventricular tachycardia that may cause sudden death. Hypomagnesemia is also associated with prolonged QTc and lethal dysrhythmias [9], [14], [38]. Moderate hyperkalemia can cause ECG changes, while severe hyperkalemia, due to the suppression of the electrical activity of the myocardium, may cause cardiac arrest. Additionally, free fluoride ions activate myocardial adenylyl cyclase thus increasing cyclic adenosine monophosphate (cAMP), which stimulates the myocardium inducing refractory ventricular fibrillation. Severe fluoride intoxication may provoke sudden cardiac arrest with a lethal outcome [1], [2], [13], [16], [18], [19], [23].

Recurrent ventricular dysrhythmias [14] or asystolia [62] can be developed several hours after HF acid ingestion or dermal exposure, while congestive heart failure provoked by toxic myocarditis has been detected as a long-term complication, four months after the hydrofluoric acid ingestion [12].

Renal symptoms

Fluorosis causes renal dysfunction, insufficiency and renal cortical necrosis followed by hematuria, proteinuria and azotemia [9], [15], [19], [22].

Osteosceletal symptoms

As the significant amount of fluoride deposits in the bones, osteolysis caused by HF intoxication has been observed.

Neuromuscular symptoms

Intoxication caused by acute exposure to HF acid may influence the function of the neuromuscular system. Hypocalcemia and hyperkalemia cause depolarisation of nerves and muscle fibres and interfere with the normal transmission of electrical signals throughout the neurons. The intoxicated person may become anxious, confused with headaches, may have seizures, paresthesia, paresis and paralysis [9], and may develop carpopedal and generalised tetany. When exposed to high doses, brain oedema followed by deep coma may occur [15], [16], [19].

Immediate, Decontamination/ Neutralization Procedures and Hospital Medical Treatment of the HF-Exposed Person

Correct diagnosis and timely treatment are of great importance when one is exposed to HF acid. Before starting any procedure, the exposed person should be checked for regular respiration and pulse, and in the case of suspected trauma, cervical immobilisation with a cervical collar and a backboard should be conducted. Decontamination implemented within the first minute and topical treatment including the use of the antidote is a critical procedure to prevent or minimise on-going HF absorption and progressive tissue destruction caused by fluoride ions [44].

Sometimes, systemic support by qualified medical staff should be obtained [54]. Immediate transport to the hospital is mandatory for the decontaminated person who has been in contact with the concentrated HF acid solutions/ vapours, if exposure to the low HF concentration lasted longer, still having acute symptoms or systemic complications are expected (no matter of the route of exposure). During the transport, skin and eye irrigation should continue, assistant ventilation if breathing has stopped and cardiopulmonary resuscitation (CPR) in the case of cardiac arrest should be given. The person who has been exposed to HF fumes only, and does not have any symptoms of skin/eyes burns, should be transported to the hospital as well and held for observation for at least 24 hours, the period when swelling of the respiratory tract is expected [24],[25],[26].

Treatment of the HF skin burns

Decontamination is mandatory for the victims with the dermal or ocular contact; contaminated clothing, as well as jewellery that could trap HF, should be immediately removed and double-bagged [31]. There are several methods that can be used for decontamination and neutralisation of the exposed skin and hair: rinsing with water, saline or solution of soap and water, and neutralisation performed with calcium gluconate, benzalkonium chloride, polyethylene glycol, magnesium oxide or Hexafluorine.

Rinsing with cold or warm (16°C) running water [29], [31], [33], [45], [51], [56], [59] or saline, for at least 30 minutes is the most commonly used decontaminating procedure. A solution of soap and water which should have a pH value of at least 8 (should not exceed a pH value of 10.5), is also recommended to neutralise low pH of the HF acid [52], using a soft brush and moving in a downward motion (from head to toe). Five per cent solution of

sodium bicarbonate can be successfully used as well [45]. Rinsing should be thoroughly performed until the contaminant is removed [4]. Ice pack on the affected area may reduce symptoms by vasoconstriction it provokes and retarding diffusion of the ion into the bloodstream [4]. Special attention should be paid when decontaminating children or the elderly because of the risk of hypothermia (blankets or warmers may be used) [4], [24].

Calcium gluconate (CaG) in its various formulations (solution, gel or ointment), administered immediately, is used as the most appropriate antidote when one is exposed to hydrofluoric acid. Sterile gauze moistened with 10% solution of calcium gluconate may be used to cover burn areas [45]. When used as a gel, 2.5 % CaG should be applied and rubbed into the affected area for 15-30 minutes [25], [40], wearing a new pair of chemical resistant gloves in order to prevent possible secondary HF burns [26]; upon reaction with the acid and forming CaF_2 precipitate, CaG gel turns white. The gel should be re-applied, every 10-15 minutes until the ambulance arrives or a physician gives medical treatment [26]. If used as a definitive treatment, 2.5% calcium gluconate should be applied 4 to 6 times daily, for 3 to 4 days [24]. Used as an ointment, it should be applied every two hours [51]. Application of surgical jelly consisting of 50% calcium gluconate and 50% dimethyl sulphoxide is recommended as well [29].

An iced solution of 0.13 % benzalkonium chloride can be used for immersion or as soaked compresses for at least 2 hours (a total of 4 to 6 hours); compresses should be changed or soaked with additional solution approximately every 2 to 4 minutes [5], [49]. This solution should not be used for burns of the face, ears or other sensitive areas.

Other useful agents are polyethylene glycol, magnesium oxide [59], 5% sodium bicarbonate [45], and Hexafluorine solution [48], [64].

Different agents have different ability in skin decontamination, neutralisation of the fluoride ion and minimising on-going HF absorption. According to Dennerlein et al. [65], polyethylene glycol reduces the cumulative penetrated amount of fluoride in the skin by 28%, flushing with water by 49%, while rinsing with CaG or Hexafluorine© is the most effective method with a reduction rate of 64% [65].

Rinsing the 20-sec exposed skin to 70% HF, with running tap water for 15 min followed by one topical application of 2.5% CaG gel, has limited preventive effect over the integrity of the cellular structure in the epidermis and the papillary and reticular dermis. Recovery, after the initial cellular deteriorations, observed 1h after the exposure, turned into edematous changes in the epidermal basal layer 3 hours later. No deterioration of the structures of either the epidermis or dermis have been detected after washing the exposed skin with Hexafluorine applied as a spray of 400 ml over 10 min, whatever the time of observation was [49].

Hultén et al. [66] have not observed any differences in the electrolyte misbalance after dermal exposure to HF acid, between the Hexafluorine-treated animals and those treated with water only. Further on, Brent [67], reviewing the data from 69 relevant papers, concluded that water-based solutions are the best, widely available and inexpensive decontaminating fluids for dermal corrosive exposures [67]. However, Yoshimura et al. [59], concluded that even after a 3 hours delay, skin washing with Hexafuorine (followed by intravenous, intradermal, perilesional, and topical injunction of calcium gluconate) is beneficial in the treatment of first- to third-degree skin burns occupying approximately 10% of the TBSA, provoked by 70% HF. Decontamination with Hexafuorine has prevented the development of significant systemic toxicity which otherwise occurs when exposed to concentrated HF acid and often results with a fatal outcome [59].

Different neutralising abilities of agents are due to the different mechanism of action. Water has a mechanical rinsing and a diluting effect only; it has no active binding or chelating properties for any chemical substance, including hydrofluoric acid. As a hypotonic liquid, it cannot stop penetration of HF throughout skin layers and may enhance such penetration. Besides mechanical rinsing of the surface, a residue of fluoride ion might be still present on the skin in a sufficient quantity to provoke secondary necrosis.

Unlike water, calcium gluconate is capable of chelating the free fluoride ions, forming insoluble salts, thus neutralising their toxical effect over the cells' metabolism. A single application of CaG gel helps in delaying the onset of the skin injury and mitigating the severity of the damage, but the tissue lesions continue to evolve; this is the reason for recommendation, CaG gel to be applied multiple times [49].

Hexafluorine® has a triple effect over the HF acid-exposed skin, eye or mucous membranes. As a sterile water-solution, it has the same rinsing and diluting effect as the pure water has. As an amphoteric compound, Hexafluorine actively acts against both primary mechanisms (corrosive and cytotoxic) through which HF acid causes tissue destruction: it has a property to neutralise the H^+ ion and chelates the F^- ion. Consequently, decontamination with Hexafluorine® completely prevents cutaneous and eye tissue injuries [49], [64].

Vapour burns of the skin are treated the same as liquid HF burns [36].

Hydrogen fluoride burns are followed by intense pain that should not be suppressed with local infiltration of anaesthetic because the degree of pain is an indicator of treatment efficacy.

Topically applied, calcium gluconate has limited ability in term of chelating the F− ions that have

been already penetrated deeply into the skin tissues. In the case of large and/or deeply penetrating burns, when exposed to hydrogen fluoride concentrations greater than 50%, when the treatment is delayed, or if pain-relief is not achieved by previously applied CaG, subcutaneous injection of sterile aqueous calcium gluconate solution underneath the burned area and into the immediately adjacent skin should improve the neutralizing efficacy [29], [30], [52], [59], [68]; the recommended dose is limited to 0.5 mL/cm^2 affected skin surface area of a 5% or 10% calcium gluconate solution (with a maximum of 0.5 mL per digit for finger burns), using a small gauge needle (#30) [29]. However, multiple injections into the fingers may lead to increased tissue pressure thus worsening an existing swelling, impairing circulation and causing ischemic necrosis [69]. It is recommended subcutaneous injection to be applied, only if there is a central grey burn with surrounding erythema, or when having severe throbbing pain [70].

According to De Capitani et al. [51], "intra-arterial calcium gluconate might be considered for finger burns caused by highly concentrated HF, when topical treatment is considered useless, or when intradermal and subcutaneous calcium injections cannot be performed" [51].

Calcium gluconate gel is not effective in treating burns of the nails as well. It may be necessary to drill, split or even remove nails to allow the topical methods of treatment to be effective [29], [30], [68]. Sometimes, removing the nails may be avoided by immediate immersion in benzalkonium chloride (Zephrian®) solution [24], [25].

The skin blisters, if already formed, should be opened and necrotic tissue should be debrided as soon as possible, as early debridement may facilitate healing [59]. There are several chirurgical methods which can be used for the treatment of the severe HF dermal burns: escharotomy or fish-mouth fasciotomy followed by intravenous administration of prostaglandin in order to maintain maximal distal circulation [71], succeed by skin grafting (a split-thickness or full-thickness skin grafting) or flap transfer for wound closure and reconstruction [1]. In case of deep layer finger injuries of weight bearing portions such as finger pulp, a partial toe pulp-free flap should be performed to reconstruct the digits [71].

Treatment of the eye burns

After ocular exposure or irritation, the eyes should be immediately irrigated with a large amount of gently flowing cool plain water or sterile 0.9 % saline solution for 15-30 minutes [45], while holding eyelids apart, and moving the eyeball in every direction, thus ensuring the irrigator reaches all the surfaces. If the exposed person is wearing contact lenses, the lenses should be carefully removed [5], [24], [26]. If sterile 1% calcium gluconate solution is available, water washing may be limited to 5 minutes.

Usage of 1-10% sterile aqueous solution of calcium-gluconate eye-drops [23], [33], [34], [45], although widely recommended as a preferred flushing agent, should be done with great care, because sometimes it may worsen the clinical outcome [4], [32].

Subconjunctival injection of a 1% CaG has been successfully used as well [25].

An in-vitro study revealed that 20% solution of mannitol used for 15 min immediately after the corneal HF exposure is an effective decontaminating agent [72].

According to Spöler et al. [55], Hexafluorine is the only decontaminating solution that preserves the transparency of the corneal surface, with no reported injuries or long-term consequences [55]. A five-year follow-up study revealed that chemical burns have not developed, nor further medical or surgical treatments have been needed in workers sustained an eye or skin HF splashes when treated with Hexafluorine [64]. According to Soderberg et al. [73], medical treatment other than initial decontamination with Hexafluorine is not required in workplaces where water decontamination followed by calcium gluconate injunction failed to prevent HF dermal and ocular burns and systemic toxicity [73].

One or two drops of proparacaine or tetracaine should provide rapid-onset ocular anaesthesia for 20 minutes to an hour, as severe pain is felt when erosion or corneal ulcer have already occurred. Corneal damage should be treated by an ophthalmologist.

Treatment after HF acid ingestion

When HF solution is ingested, it is very dangerous to induce vomiting. Instead, if the exposed person is conscious, his/her mouth should be thoroughly rinsed with water or with a 5-10% solution of calcium gluconate [9], [45].

Gastric suction and lavage using a small flexible nasogastric tube are recommended within the first hour of ingestion [11] if a large dose of HF solution has been ingested or the patient has oral lesions or persistent oesophagal discomfort. Large amounts of room temperature water, milk (120-240 ml), 10% CaG, magnesium-containing beverages (60-120 ml) as well as 60 gr sodium polystyrene sulfonate should be taken orally or by nasogastric tube in order to dilute the acid and bind the remaining fluoride ions that have not been absorbed yet [9], [11], [24], [25], [26]. Anyway, good assessment should be done if using a nasogastric tube excludes the risk of oesophagal or gastric perforation [9].

According to Heard and Delgado [39], oral administration of calcium- or magnesium-containing

solutions does not alter the toxic effect following hydrofluoric acid ingestion. It is forbidden to administrate sodium bicarbonate to neutralise the acid, as the carbon dioxide byproduct could cause severe burns [39].

Endoscopy may be performed to define the extent of the injury, to assess the state of mucous membrane and to prognosticate the course of recovery [11]. However, this procedure should be performed after the neutralisation of the HF acid content into the stomach, as the HF destroys optic fibres while attempting endoscopic examination [25].

Treatment after HF inhalation

After inhalation of HF gases, fumes or vapours, the affected person should be immediately moved to fresh air. One hundred per cent oxygen (10 to 12 L/min flow rate) should be administered as soon as possible [45], and a bag-valve-mask for assistant ventilation can be used if breathing has stopped [24].

Calcium gluconate solution, 2.5% - 5%, given by intermittent positive-pressure ventilation using a nebuliser is the therapy of choice when starting the hospital treatment [17], [56]. Aerosolised bronchodilator should be administered in the patients with bronchospasm considering the myocardial condition; the risk of cardiac arrhythmias (especially in the elderly) should be estimated. Racemic epinephrine aerosol (0.25–0.75 mL of 2.25% racemic epinephrine solution in 2.5 cc water), repeated every 20 minutes if needed, might be useful for children who developed stridor [5], [24]. In the case of pulmonary oedema, calcium gluconate and N-Acetyl cysteine given intravenously on the first day and with a nebuliser for 48 h after the exposure have been proved to be efficient in reducing the pulmonary secretion [57]. Aspiration and lavage of the affected bronchi [45] or lungs [3] may also be performed.

If the respiration is compromised (in case of oedema, laryngospasm and hypoxemia), an airway may be secured via endotracheal intubation [11], [19], cricothyroidotomy or tracheotomy [35], [45], while the respiratory function should be established by mechanical ventilation.

Fiberoptic bronchoscopy is a prognostic procedure that is performed to assess the extent of damage to the respiratory tract and to evaluate the efficacy of the conducted therapy [3].

Systemic toxicity treatment

As mentioned before, the fluoride is a low-molecular-weight anion that is easily absorbed through the skin, mucous membranes of the gastrointestinal and respiratory tracts, diffusing readily into the bloodstream causing fluorosis and acidosis, hypocalcemia, hypomagnesemia and hyperkalemia or hypokalemia [2], [61], [62]. The half-life of fluoride is 12 to 24 hours and is eliminated primarily through renal excretion. Because of its highly toxic potential, increasing the renal elimination by administrating diuretic therapy and alkalization of the urine with sodium bicarbonate are of great importance [45].

Even if the serum electrolytes and blood saturation with oxygen are already normalised, recurrent ventricular fibrillation may still occur. It is assumed that the reason is fluoride-induced cardiotoxicity due to the high fluoride levels in the serum and urine. In such cases, hemodialysis enables full recovery of the intoxicated person [58]. Continuous renal replacement therapy, hemofiltration or hemodialysis, should be conducted as an effective and potentially lifesaving treatment in patients with severe systemic toxicity [23], [45], [60]. Antar-Shultz et al. [37], have confirmed 70% reduction of the fluoride level in the blood after three hours of hemodialysis, with the recommendation, the initial hemodialysis to be prolonged beyond the standard four-hour treatment session [37]. Continuous venovenous hemodialysis up to 72 hours followed by continuous venovenous hemofiltration up to 10 days has been performed to remove delayed release of fluoride ions to avoid fluoride-related cardiac toxicity [45].

According to Pu et al., “cardiac arrhythmia is the leading cause of death during the early stage, mainly due to polymorphic ventricular tachycardia and ventricular dysrhythmias” [45]. Hypocalcemia is considered as the main factor that provokes disturbances in the cardiac rhythm. Therefore calcium-containing substances are mainstays of therapy for fluoride toxicity [11]. Normal calcium level can be achieved by ordering intravenous (IV) infusions of 10% calcium gluconate [74], [75], [76], with doses of 0.1 to 0.2 mL/kg. Infusions can be repeated until serum calcium, ECG, or symptoms improve. If hand or forearm is affected, Hatzifotis et al. [29] recommended regional IV infusion of 40 ml 10% CaG with 5000 U heparin. Pu et al. [45] in a person with severe cutaneous injuries involving approximately 60% of the TBSA (with third-degree burns present on approximately 13% of the burn area), provoked by 10% HF and 50% nitric acid, after an initial 20mL IV bolus of 10% CaG, continued the infusion with 6 g/h until ultimate normalization of calcemia and stabilization of the cardiac rhythm (a total of 55g of CaG during the first 24 hours) [45]. A total of 8.4 gr of elemental calcium administered as 10% calcium gluconate at 20 mL/h, is a dosage that has normalised Ca level when ingested 120 ml of 20-25% HFA [11].

Intra-arterial infusion of calcium gluconate, firstly reported by Köhnlein and Achinger [50], is indicated when exposed to high HF concentrations with severe burns [51], rapid destruction of tissues and acute systemic toxicity especially in patients with upper and lower extremities- and facial burns [29], [30], [63], [77], [78]. According to ASTDR, the initial dosage is 10 mL of 10% calcium gluconate diluted

with 40 mL D_5W given intra-arterially over 4 hours. If the pain is unrelieved, 20% concentrations should be used. The ultimate goal is achieving a pain-free condition for up to 4 hours [24].

Nguyen et al. [79] reported a case of calcium gluconate infusion via the external carotid artery in a person with severe face burn. When severe burns of the digits, the brachial or the radial artery [51], [77], [80] are catheterised, depending on the fingers involved [53]. Intra-arterial infusions of 2% CaG solution in 5% dextrose have been given through radial artery at wrist level, every four hours for 36 hours when burned middle and fourth fingers with 70% HF acid [51]. Pain symptoms have been improved and sensory, and motor functions have been restored in the fingers D II to D V injured with 60% HFA, after intra-arterial infusion of 10 ml 20% CaG in 40 ml 0.9 % NaCl administered over 4 hours. Thomas et al. [63] concluded that intra-arterial calcium gluconate injection is a successful and well-tolerated therapy for HF burn of the hand associated with Raynaud's syndrome [63]. Vasospasm of the common palmar digital artery has been eliminated by vasoactive therapy with alprostadil while platelet aggregation has been inhibited with acetylsalicylic acid and clopidogrel [53].

However, a great precaution and Intensive Care Unit (ICU) monitoring is required when ordering intra-arterial infusion (in terms of infusion solution, concentration, and time interval) as some serious complications may occur including artery spasm and bleeding, hematomas followed by median nerve palsies, carpal tunnel syndrome, hypercalcemia and even a high morbidity when brachial artery-cannulation [23].

Hypomagnesemia, associated with a prolonged QTc and possible lethal dysrhythmias, can be solved by 2 to 4 mL of 50% of magnesium sulfate intravenously, over 40 minutes [4], [24], [61], [62], [74], or continuous IV infusion of 25% magnesium sulfate at 1.5 g/h according to the concentration of serum magnesium [11], [45].

Hyperkalemia, provoking ECG disturbances or cardiac arrest, should be treated with calcium gluconate (10-20 ml of 10% solution IV) to protect myocardium, in conjunction with 10 U of regular insulin intravenously administered along with 50 mL of 50% dextrose (or glucose) [11] to enhance shifting potassium from the vascular space into the cells; 10-20 mg (5 mg/ml) Albuterol (Ventolin) administered by nebulizer, has additive effect to that of insulin, while 20-40 mg Furosemide (Lasix) IV, increases renal excretion of potassium, thus, both of them, decreasing the free potassium level. Sodium bicarbonate administered intravenously as 8.4 % solution and 60 g sodium polystyrene sulfonate given via the nasogastric tube or in 30 ml of sorbitol solution administered orally (in the case of HFA ingestion), removes potassium from the blood or gastrointestinal tract in exchange for sodium [11].

Patients with a life-threatening condition (substantial skin burns, persistent hypotension, respiratory distress, cardiac arrhythmias, seizures and coma) should be admitted at an intensive care unit [30], and treated according to Advanced Life Support (ALS) protocol.

In the case of ventricular fibrillation, defibrillation should be conducted, as many times as needed [11], [14], [45] and administrate dobutamine to improve left ventricular contraction. If acute respiratory distress syndrome (ARDS) appears, and routine mechanical ventilation or higher level of applied positive end-expiratory pressure (PEEP) cannot improve oxygenation, extracorporeal membrane oxygenation (ECMO) is a method for relief from hypoxemia and/or carbon dioxide retention [45], [57].

Additionally, glucocorticoid (methylprednisolone 40mg/8h) and antibiotic to prevent bacterial infection should be administered [35], [45].

Unfortunately, when exposed to high concentration of HFA solution (50% and higher), with extensive and deep skin burns (third-degree), even a vigorous medical treatment consisted of a continuous administration of calcium gluconate (50 ml/h, 8,5% solution) and magnesium sulfate, a massive transfusion of saline with catecholamine (vasopressor) for the treatment of shock, Midazolam (2 mg), vecuronium (8 mg), and buprenorphine (0.2 mg), extensive skin debridement and even leg amputation in order to prevent HFA flowing into systemic circulation, defibrillation and cardiopulmonary resuscitation could not stop the progression of disseminated intravascular coagulation that eventually lead to cardiopulmonary arrest, progressive organ damage and lethal outcome [19].

Conclusion

Due to its high reactivity, hydrofluoric acid is a commonly used the chemical compound in many industrial branches and as a domestic cleaning agent. It possesses corrosive potential causing burns and tissue necrosis on the site of contact, while when absorbed into the bloodstream and distributed to all organs and tissues, it provokes potential life-threatening systemic toxicity and organs failure. All this imposes an extraordinary caution and great awareness of health consequences when using, and implementation of all personal and general protective measures.

The kinetics of the fluoride ion penetration into the skin and mucous membrane and organ distribution imposes appropriate urgent first aid and

secondary medical management. Initial decontamination procedures started within the first minute after the exposure, neutralisation and antidote agents implemented promptly are of great importance to avoid or minimise the extent and depth of local tissue damage or necrosis, as well as to prevent absorption and systemic distribution of the fluoride ions and massive systemic electrolyte imbalance. Electrolyte replacement therapy including calcium gluconate and magnesium sulfate, fluid resuscitation, bronchodilators, glucocorticoids and antibiotics, vasopressors, in conjunction with insulin, furosemide and anticoagulants, are medicines of choice. Extracorporeal membrane oxygenation used to improve oxygenation and to support hemodynamic profile in case of acute respiratory distress syndrome or cardiac arrest, as well as renal replacement therapy, to remove serum fluorides and excess potassium, are sometimes necessary procedures to sustain life in severe fluoride intoxication.

References

1. Zhang Y, Zhang J, Jiang X, Ni L, Ye C, Han C, Sharma K, Wang X. Hydrofluoric acid burns in the western Zhejiang Province of China: a 10-year epidemiological study. J Occup Med Toxicol. 2016 11:55. https://doi.org/10.1186/s12995-016-0144-3 PMid:27980604 PMCid:PMC5142164

2. Wu ML, Yang CC, Ger J, Tsai WJ, Deng JF. Acute hydrofluoric acid exposure reported to Taiwan Poison Control Center, 1991-2010. Hum Exp Toxicol. 2014; 33(5):449-54. https://doi.org/10.1177/0960327113499165 PMid:23892993

3. Kim YJ, Shin JY, Kang SM, Kyung SY, Park J-W, Lee SP, Lee SM, Jeong SH. Pulmonary alveolar proteinosis induced by hydrofluoric acid exposure during fire extinguisher testing. J Occup Med Toxicol. 2015; 10(6):1-3. https://doi.org/10.1186/s12995-015-0048-7

4. Hydrogen Fluoride/Hydrofluoric Acid: Systemic Agent. Center for Disease, Control and Prevention. The National Institute for Occupational Safety and Health (NIOSH). https://www.cdc.gov/niosh/ershdb/emergencyresponsecard_29750030.html Accessed August 20, 2018

5. Recommended Medical Treatment for Hydrofluoric Acid Exposure. Honeywell International Inc. 2018:1-23.

6. Ho GW, Matinlinna JP. Insights on ceramics as dental materials. Part II: chemical surface treatments. Silicon. 2011; 3:117-23. https://doi.org/10.1007/s12633-011-9079-6

7. Blatz MB, Sadan A, Kern M. Resin-ceramic bonding: a review of the literature. J Prosthet Dent. 2003; 89(3):268-74. https://doi.org/10.1067/mpr.2003.50 PMid:12644802

8. Bajraktarova-Valjakova E, Grozdanov A, Guguvcevski Lj, Korunoska-Stevkovska V, Kapusevska B, Gigovski N, Mijoska A, Bajraktarova-Misevska C. Acid etching as surface treatment method for luting of glass-ceramic restorations, part 1: Acids, application protocol and etching effectiveness. Open Access Maced J Med Sci. 2018; 6(3):568-73. https://doi.org/10.3889/oamjms.2018.147 PMid:29610622 PMCid:PMC5874387

9. Makarovsky I, Markel G, Dushnitsky T, Eisenkraft A. Hydrogen fluoride - the protoplasmic poison. Isr Med Assoc J. 2008; 10(5):381-5. PMid:18605366

10. Franzblau A, Sahakian N. Asthma following household exposure to hydrofluoric acid. Am J Ind Med. 2003; 44(3):321-4. https://doi.org/10.1002/ajim.10274 PMid:12929153

11. Whiteley PM, Aks SE. Case files of the Toxikon Consortium in Chicago: survival after intentional ingestion of hydrofluoric acid. J Med Toxicol. 2010; 6(3):349-54. https://doi.org/10.1007/s13181-010-0088-4 PMid:20661686 PMCid:PMC3550485

12. Gradinger R, Jung C, Reinhardt D, Mall G, Figulla HR. Toxic myocarditis due to oral ingestion of hydrofluoric acid. Heart Lung Circ. 2008; 17(3):248-50. https://doi.org/10.1016/j.hlc.2007.04.011 PMid:17822953

13. Ozsoy G, Kendirli T, Ates U, Perk O, Azapagasi E, Ozcan S, Baran C, Goktug A, Dindar H. Fatal refractory ventricular fibrillation due to ingestion of hydrofluoric acid. Pediatr Emerg Care. 2018. https://doi.org/10.1097/PEC.0000000000001548 PMid:30020244

14. Vohra R, Velez LI, Rivera W, Benitez FL, Delaney KA. Recurrent life-threatening ventricular dysrhythmias associated with acute hydrofluoric acid ingestion: observations in one case and implications for mechanism of toxicity. Clin Toxicol (Phila). 2008; 46(1):79-84. https://doi.org/10.1080/15563650701639097 PMid:17906993

15. Ohtani M, Nishida N, Chiba T, Muto H, Yoshioka N. Pathological demonstration of rapid involvement into the subcutaneous tissue in a case of fatal hydrofluoric acid burns. Forensic Sci Int. 2007; 167(1):49-52. https://doi.org/10.1016/j.forsciint.2005.12.008 PMid:16426786

16. Martínez MA, Ballesteros S, Piga FJ, Sánchez de la Torre C, Cubero CA. The tissue distribution of fluoride in a fatal case of self-poisoning. J Anal Toxicol. 2007; 31(8):526-33. https://doi.org/10.1093/jat/31.8.526 PMid:17988468

17. Zierold D, Chauviere M. Hydrogen fluoride inhalation injury because of a fire suppression system. Mil Med. 2012; 177(1):108-12. https://doi.org/10.7205/MILMED-D-11-00165 PMid:22338991

18. Smędra-Kaźmirska A, Kędzierski M, Barzdo M, Jurczyk A, Szram S, Berent J. Accidental intoxication with hydrochloric acid and hydrofluoric acid mixture. Arch Med Sadowej Kryminol. 2014; 64(1):50-8. https://doi.org/10.5114/amsik.2014.44590 PMid:25184427

19. Onohara T, Komine M, Yoshidomi Y, Amari K, Fujita R, Matsumoto Y, Koyama T, Koga M, Mitsumizo S, Satake Y, Masumoto K, Matsunaga T, Mae T, Fujita N. Chemical burn caused by high-concentration hydrofluoric acid: a case that followed a lethal course. Glob Dermatol. 2015; 2(6):215-7.

20. Blodgett DW, Suruda AJ, Crouch BI. Fatal unintentional occupational poisonings by hydrofluoric acid in the U.S. Am J Ind Med. 2001; 40(2):215-20. https://doi.org/10.1002/ajim.1090 PMid:11494350

21. Bertolini JC. Hydrofluoric acid: a review of toxicity. J Emerg Med. 1992; 10(2):163-8. https://doi.org/10.1016/0736-4679(92)90211-B

22. Özcan M, Allahbeickaraghi A, Dündar M. Possible hazardous effects of hydrofluoric acid and recommendations for treatment approach: a review. Clin Oral Investig. 2012; 16(1):15-23. https://doi.org/10.1007/s00784-011-0636-6 PMid:22065247

23. McKee D, Thoma A, Bailey K, Fish J. A review of hydrofluoric acid burn management. Plast Surg (Oakv). 2014; 22(2):95-8. https://doi.org/10.1177/229255031402200202

24. Hydrogen Fluoride. Agency for Toxic Substances and Disease Registry ATSDR, Federal public health agency of the U.S. Department of Health and Human Services: 1-23. https://www.atsdr.cdc.gov/mhmi/mmg11.pdf Accessed August 10, 2018.

25. Emergency response guidelines for anhydrous hydrogen fluoride (HF). American Chemistry Council. August 2007. 1-58. https://www.americanchemistry.com/ProductsTechnology/Hydrogen-Fluoride-2/Emergency-Response-Guidelines-for-AHF.pdf Accessed August 15, 2018.

26. Guidelines for the safe use of hydrofluoric acid. Harvard University, Department of Chemistry and Chemical Biology. Cambridge, MA, USA. February 2013:1-8.

https://chemistry.harvard.edu/files/chemistry/files/safe_use_of_hf_0.pdf Accessed August 10, 2018.

27. http://www.ivoclarvivadent.us/zoolu-website/media/document/4176/IPS+Ceramic +Etching+ gel+ (document last reviewed on 04/14/2016). Accessed May 1, 2016.

28. Bartlett D. Dermal exposure to hydrofluoric acid causing significant systemic toxicity. J Emerg Nurs. 2004; 30(4):371-3. https://doi.org/10.1016/j.jen.2004.06.014 PMid:15282524

29. Hatzifotis M, Williams A, Muller M, Pegg S. Hydrofluoric acid burns. Burns. 2004; 30(2):156-9. https://doi.org/10.1016/j.burns.2003.09.031 PMid:15019125

30. Stuke LE, Arnoldo BD, Hunt JL, Purdue GF. Hydrofluoric acid burns: a 15-year experience. J Burn Care Res. 2008; 29(6):893-6. https://doi.org/10.1097/BCR.0b013e31818b9de6 PMid:18849854

31. Barker L. Hydrofluoric acid skin exposure. Nursing. 2012; 42(6):72. https://doi.org/10.1097/01.NURSE.0000414644.43323.66 PMid:22627830

32. Wang X, Zhang Y, Ni L, You C, Ye C, Jiang R, Liu L, Liu J, Han C. A review of treatment strategies for hydrofluoric acid burns: current status and future prospects. Burns. 2014; 40(8):1447-57. https://doi.org/10.1016/j.burns.2014.04.009 PMid:24946967

33. Atley K, Ridyard E. Treatment of hydrofluoric acid exposure to the eye. Int J Ophthalmol. 2015; 8(1):157-61. PMid:25709926 PMCid:PMC4325260

34. Bentur Y, Tannenbaum S, Yaffe Y, Halpert M. The role of calcium gluconate in the treatment of hydrofluoric acid eye burn. Ann Emerg Med. 1993; 22(9):1488-90. https://doi.org/10.1016/S0196-0644(05)82003-7

35. Kawaura F, Fukuoka M, Aragane N, Hayashi S. Acute respiratory distress syndrome induced by hydrogen fluoride gas inhalation. Nihon Kokyuki Gakkai Zasshi. 2009; 47(11):991-5. PMid:19994593

36. Siéwé C-L, Barbe J-M, Mathieu L, Blomet J, Hall AH. Hexafluorine decontamination of 70% hydrofluoric acid (HF) vapor facial exposure: Case report. J Chem Health Saf. 2012; 19(1):7-11. https://doi.org/10.1016/j.jchas.2011.05.011

37. Antar-Shultz M, Rifkin SI, McFarren C. Use of hemodialysis after ingestion of a mixture of acids containing hydrofluoric acid. Int J Clin Pharmacol Ther. 2011; 49(11):695-9. https://doi.org/10.5414/CP201532 PMid:22011695

38. Kavakli AS, Ozturk NK. Recurrent ventricular fibrillation associated with acute ingestion of hydrofluoric acid. J Clin Anesth. 2018; 46:8-9. https://doi.org/10.1016/j.jclinane.2018.01.009 PMid:29320713

39. Heard K, Delgado J. Oral decontamination with calcium or magnesium salts does not improve survival following hydrofluoric acid ingestion. J Toxicol Clin Toxicol. 2003; 41(6):789-92. https://doi.org/10.1081/CLT-120025343 PMid:14677788

40. Upfal M, Doyle C. Medical management of hydrofluoric acid exposure. J Occup Med. 1990; 32(8):726-31. PMid:2401930

41. Hydrogene Fluoride. In: Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 4. Committee on Toxicology, National Research Council (US). National Academies Press (US) Washington, D.C.; 2004:123-98. https://www.ncbi.nlm.nih.gov/books/NBK207733/

42. Bosse GM, Matyunas NJ. Delayed toxidromes. Emerg J Med. 1999; 17(4):679-90. https://doi.org/10.1016/S0736-4679(99)00064-5

43. https://inis.iaea.org/collection/NCLCollectionStore/_Public/16/077/16077051.pdf

44. Burgher F, Mathieu L, Lati E, Gasser P, Peno-Mazzarino L, Blomet J, Hall AH, Maibach HI. Experimental 70% hydrofluoric acid burns: histological observations in an established human skin explants ex vivo model. Cutan Ocul Toxicol. 2011; 30(2):100-7. https://doi.org/10.3109/15569527.2010.533316 PMid:21077748 PMCid:PMC3116716

45. Pu Q, Qian J, Tao W, Yang A, Wu J, Wang Y. Extracorporeal membrane oxygenation combined with continuous renal replacement therapy in cutaneous burn and inhalation injury caused by hydrofluoric acid and nitric acid. Medicine. 2017; 96(48):e8972. https://doi.org/10.1097/MD.0000000000008972 PMid:29310404 PMCid:PMC5728805

46. Kilo S, Dennerlein K, Korinth G, Göen T, Drexler H. Dermal absorption of fluoride and hydrogen ions following topical exposure to hydrofluoric acid. Occup Environ Med. 2018; 75(Suppl 2):A409.

47. Dennerlein K, Kiesewetter F, Kilo S, Jäger T, Göen T, Korinth G, Drexler H. Dermal absorption and skin damage following hydrofluoric acid exposure in an ex vivo human skin model. Toxicol Lett. 2016; 248:25-33. https://doi.org/10.1016/j.toxlet.2016.02.015 PMid:26930472

48. Mathieu L, Burgher F, Constant S, Huang S, Hall AH, Blomet J, Fortin J-L, Schrage NF. Hydrofluoric acid: update about knowledge on eye/skin and respiratory exposure damages and decontamination. Occup Environ Med. 2018; 75(Suppl 2):A19.

49. Burgher F, Mathieu L, Lati E, Gasser P, Peno-Mazzarino L, Blomet J, Hall AH, Maibach HI. Part 2. Comparison of emergency washing solutions in 70% hydrofluoric acid-burned human skin in an established ex vivo explants model. Cutan Ocul Toxicol. 2011; 30(2):108-15. https://doi.org/10.3109/15569527.2010.534748 PMid:21083510 PMCid:PMC3116720

50. Köhnlein H, Achinger R. A new method of treatment of hydrofluoric acid burns of the extremities. Chir Plast. 1982; 6(4):297-305. https://doi.org/10.1007/BF00288763

51. De Capitani EM, Hirano ES, Zuim Ide S, Bertanha L, Vieira RJ, Madureira PR, Bucaretchi F. Finger burns caused by concentrated hydrofluoric acid, treated with intra-arterial calcium gluconate infusion: case report. Sao Paulo Med J. 2009; 127(6):379-81. https://doi.org/10.1590/S1516-31802009000600011

52. Park SE, Lee JY, Kim CW, Kim SS. Hydrofluoric acid burn on a fingertip treated successfully with single session of subcutaneous injection of 6.7% Calcium Gluconate. Ann Dermatol. 2016; 28(5):639-40. https://doi.org/10.5021/ad.2016.28.5.639 PMid:27746647 PMCid:PMC5064197

53. Peter J, Maksan S-M, Eichler K, Schmandra TC, Schmitz-Rixen T. Hydrofluoric acid burn of the hand – a rare emergency. Eur J Vasc Endovasc Surg. 2012; 24(4):e19-e20.

54. Wedler V, Guggenheim M, Moron M, Künzj W, Meyer VE. Extensive hydrofluoric acid injuries: a serious problem. J Trauma. 2005; 58(4):852-7. https://doi.org/10.1097/01.TA.0000114528.15627.65 PMid:15824669

55. Spöler F, Frentz M, Först M, Kurz H, Schrage NF. Analysis of hydrofluoric acid penetration and decontamination of the eye by means of time-resolved optical coherence tomography. Burns. 2008; 34(4):549-55. https://doi.org/10.1016/j.burns.2007.05.004 PMid:17869429

56. Kono K, Watanabe T, Dote T, Usuda K, Nishiura H, Tagawa T, Tominaga M, Higuchi Y, Onnda M. Successful treatments of lung injury and skin burn due to hydrofluoric acid exposure. Int Arch Occup Environ Health. 2000; 73 Suppl:S93-7. https://doi.org/10.1007/PL00014634 PMid:10968568

57. Shin JS, Lee S-W, Kim N-H, Park J-S, Kim KJ, Choi S-H, HongY-S. Successful extracorporeal life support after potentially fatal pulmonary oedema caused by inhalation of nitric and hydrofluoric acid fumes. Resuscitation. 2007; 75(1):184–8. https://doi.org/10.1016/j.resuscitation.2007.04.004 PMid:17507140

58. Björnhagen V, Höjer J, Karlson-Stiber C, Seldén AI, Sundbom M. Hydrofluoric acid-induced burns and life-threatening systemic poisoning - favorable outcome after hemodialysis. J Toxicol Clin Toxicol. 2003; 41(6):855-60. https://doi.org/10.1081/CLT-120025351 PMid:14677796

59. Yoshimura CA, Mathieu L, Hall AH, Monteiro MG, de Almeida DM. Seventy per cent hydrofluoric acid burns: delayed decontamination with hexafluorine® and treatment with calcium gluconate. J Burn Care Res. 2011; 32(4):e149-54. https://doi.org/10.1097/BCR.0b013e31822240f7 PMid:21747332

60. Zhang Y, Wang X, Liu Y, Jiang X, Ye C, Ni L, Zhang L, Zhang J, Xu B, Han C. Management of a rare case with severe hydrofluoric acid burns: important roles of neutralizers and continuous renal replacement therapy. Int J Low Extrem Wounds. 2017; 16(4):289-295. https://doi.org/10.1177/1534734617736198 PMid:29132247

61. Dalamaga M, Karmaniolas K, Nikolaidou A, Papadavid E. Hypocalcemia, hypomagnesemia, and hypokalemia following hydrofluoric acid chemical injury. J Burn Care Res. 2008; 29(3):541-3. https://doi.org/10.1097/BCR.0b013e3181711152 PMid:18388571

62. Wu ML, Deng JF, Fan JS. Survival after hypocalcemia, hypomagnesemia, hypokalemia and cardiac arrest following mild hydrofluoric acid burn. Clin Toxicol (Phila). 2010; 48(9):953-5. https://doi.org/10.3109/15563650.2010.533676 PMid:21171855

63. Thomas D, Jaeger U, Sagoschen I, Lamberti C, Wilhelm K. Intra-arterial calcium gluconate treatment after hydrofluoric acid burn of the hand. Cardiovasc Intervent Radiol. 2009; 32(1):155-8. https://doi.org/10.1007/s00270-008-9361-1 PMid:18506520

64. Mathieu L, Nehles J, Blomet J, Hall AH. Efficacy of hexafluorine for emergent decontamination of hydrofluoric acid eye and skin splashes. Vet Hum Toxicol. 2001; 43(5):263-5. PMid:11577928

65. Dennerlein K, Hahn T, Göen T, Drexler H, Kilo S. Hydrofluoric acid – effects of skin decontamination on the bioavailability of fluoride. Occup Environ Med. 2018; 75 (Suppl 2):A408-A409.

66. Hultén P, Höjer J, Ludwigs U, Janson A. Hexafluorine vs. standard decontamination to reduce systemic toxicity after dermal exposure to hydrofluoric acid. J Toxicol Clin Toxicol. 2004; 42(4):355-61. https://doi.org/10.1081/CLT-120039541 PMid:15461243

67. Brent J. Water-based solutions are the best decontaminating fluids for dermal corrosive exposures: a mini review. Clin Toxicol (Phila). 2013; 51(8):731-6. https://doi.org/10.3109/15563650.2013.838628 PMid:24003912

68. Ohata U, Hara H, Suzuki H. 7 cases of hydrofluoric acid burn in which calcium gluconate was effective for relief of severe pain. Contact Dermatitis. 2005; 52(3):133-7. https://doi.org/10.1111/j.0105-1873.2005.00521.x PMid:15811026

69. Anderson WJ, Anderson JR. Hydrofluoric acid burns of the hand: mechanism of injury and treatment. J Hand Surg Am. 1988; 13(1):52-7. https://doi.org/10.1016/0363-5023(88)90200-6

70. Strausburg M, Travers J, Mousdicas N. Hydrofluoric acid exposure: a case report and review on the clinical presentation and management. Dermatitis. 2012; 23(5):231-6. https://doi.org/10.1097/DER.0b013e31826e457a PMid:23010832

71. Han HH, Kwon BY, Jung SN, Moon SH. Importance of initial management and surgical treatment after hydrofluoric acid burn of the finger. Burns. 2017; 43(1):e1-e6. https://doi.org/10.1016/j.burns.2016.07.031 PMid:27650188

72. Nosé RM, Daga FB, Nosé W, Kasahara N. Optical coherence tomography analysis of hydrofluoric acid decontamination of human cornea by mannitol solution. Burns. 2017; 43(2):424-8. https://doi.org/10.1016/j.burns.2016.08.012 PMid:27608526

73. Soderberg K, Kuusinen P, Mathieu L, Hall AH. An improved method for emergent decontamination of ocular and dermal hydrofluoric acid splashes. Vet Hum Toxicol. 2004; 46(4):216-8. PMid:15303400

74. Henry JA, Hla KK. Intravenous regional calcium gluconate perfusion for hydrofluoric acid burns. J Toxicol Clin Toxicol. 1992; 30(2):203-7. https://doi.org/10.3109/15563659209038631

75. Gupta R. Intravenous calcium gluconate in the treatment of hydrofluoric acid burns. Ann Emerg Med. 2001; 37(6):734-5. https://doi.org/10.1067/mem.2001.115842 PMid:11385351

76. Zhang Y, Wang X, Ye C, Liu L, Jiang R, Ni L, Xia W, Han C. The clinical effectiveness of the intravenous infusion of calcium gluconate for treatment of hydrofluoric acid burn of distal limbs. Burns. 2014; 40(4):e26-30. https://doi.org/10.1016/j.burns.2013.12.003 PMid:24418646

77. Lin TM, Tsai CC, Lin SD, Lai CS. Continuous intra-arterial infusion therapy in hydrofluoric acid burns. J Occup Environ Med. 2000; 42(9):892-7. https://doi.org/10.1097/00043764-200009000-00008 PMid:10998764

78. Yuanhai Z, Liangfang N, Xingang W, Ruiming J, Liping L, Chunjiang Y, Wenhao X, Chunmao H. Clinical arterial infusion of calcium gluconate: the preferred method for treating hydrofluoric acid burns of distal human limbs. Int J Occup Med Environ Health. 2014; 27(1):104-13. PMid:24464441

79. Nguyen LT, Mohr WJ 3rd, Ahrenholz DH, Solem LD. Treatment of hydrofluoric acid burn to the face by carotid artery infusion of calcium gluconate. J Burn Care Rehabil. 2004; 25(5):421-4. https://doi.org/10.1097/01.BCR.0000138288.15403.BA PMid:15353934

80. Miyamoto K, Shimizu M, Tanaka K, Minemura A, Tamatsukuri T, Miyake Y, Aruga T. Case of continuous trans-arterial calcium gluconate infusion using a direct arterial sphygmomanometry line that exhibited dramatic improvement of chemical burns on the fingers caused by hydrofluoric acid. Chudoku Kenkyu. 2014; 27(4):343-7. PMid:25771670