Fire smoke inhalation: mechanisms of toxicity and recommendations for management.

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MECHANISMS OF TOXICITY AND RECOMMENDATIONS FOR MANAGEMENT.
Intoxication par inhalation de fumées d’incendie
Mécanismes de toxicité et recommandations de prise en charge


Keywords: Smoke inhalation; intoxication/poisoning; carbon monoxide; cyanide; antidote; hydroxocobalamin; acute respiratory distress syndrome

ABSTRACT
Smoke inhalation causes systemic and mucosal toxicity due to the asphyxiant and irritant properties of toxic gases. It represents the first cause of death at the fire scene and after hospital admission. Carbon monoxide and cyanide are the main gases produced during combustion in fires: they are responsible for a syndrome of oxygen deprivation. In smoke inhalation victims, loss of consciousness may result from either carbon monoxide or cyanide inhalation, although differentiating the exact role of each of them remains quite impossible. The occurrence of hypotension, abnormal respiratory pattern and/or significant lactic acidosis (with plasma lactate concentration ≥10 mmol/l) is consistent with smoke inhalation-induced-cyanide poisoning. Irritant gases contained in smoke are responsible for the ocular and respiratory mucosal injuries. Dysphonia and bronchial ronchi are predictive of delayed lung injury possibly resulting in acute respiratory failure. In smoke inhalation victims, supportive treatment is the cornerstone, based on oxygen administration and aiming at treating respiratory failure. If consciousness impairment persists despite oxygen (100% FiO2), cyanide intoxication should be suspected. According to the recommendations of the European Society of Emergency Medicine, hydroxocobalamin should be early administered as first-line antidote on the scene. Its efficiency has been well-recognized and its safety well-assessed. After hospital transfer, hyperbaric oxygen should be discussed according to the severity of features attributed to carbon monoxide poisoning. In the presence of irritant gas-related lung injuries, treatment of acute respiratory distress syndrome is based on the usual critical cares. However, final outcome of fire smoke-poisoned survivors remains critical, with possible significant cognitive sequellae.

RÉSUMÉ: L’inhalation de fumées d’incendie est responsable d’une toxicité systémique et muqueuse liée respectivement à la présence de gaz asphyxiants et irritants. Il s’agit de la cause principale de décès sur le site et dans les suites d’un incendie. Le monoxyde de carbone et le cyanaure sont les principaux gaz asphyxiants produits lors d’un feu d’habitation : ils sont responsables d’un syndrome de privation en oxygène. Chez une victime d’inhalation de fumées, un trouble de conscience évoque une telle intoxication, sans pouvoir pour autant discriminer entre ces deux gaz toxiques. Par contre, la présence d’une hypotension, d’une anomalie de la ventilation et/ou d’une acidose lactique importante (supérieure ou égale à 10 mmol/L) rend fortement probable une intoxication cyanhydrique associée. L’intoxication par les multiples gaz irritants présents dans les fumées est à l’origine de lésions muqueuses oculaires et/ou respiratoires. La dysphonia et les râles bronchiques à l’auscultation doivent mettre en garde contre le risque de survenue retardée d’une bronchopneumonie avec insuffisance respiratoire aiguë. Le traitement symptomatique est la pierre angulaire de la prise en charge de toute victime d’inhalation de fumées d’incendie. Il inclut oxygénation et traitement de la défaillance respiratoire. Si le trouble de conscience persiste malgré une oxygénation avec une FiO2 de 100%, une intoxication cyanhydrique doit être suspectée. Selon les recommandations de la Société Européenne de Médecine d’Urgence, l’hydroxocobalamin est alors l’antidote de choix et doit être administré dès la prise en charge pré-hospitalière sur le site de l’incendie. Son efficacité est désormais reconnue et sa bonne tolérance bien documentée. Par la suite, une oxygénothérapie hyperbare doit être discutée en fonction de la gravité des manifestations cliniques attribuées au monoxyde de carbone. En cas de lésions pulmonaires par les gaz irritants, le traitement du syndrome de détresse respiratoire aiguë fait appel aux mesures habituelles de réanimation. Le pronostic final d’un patient survivant après une intoxication par fumées d’incendie reste réservé, en raison de possibles séquelles, notamment cognitives.

Mots-clés : Fumées d’incendie ; intoxication ; monoxyde de carbone ; cyanure ; antidote ; hydroxocobalamin ; syndrome de détresse respiratoire aiguë
INTRODUCTION

Residential fires cause the vast majority of victims whereas warehouse fires cause often simple material losses (1). In fact, fires are the cause of smoke poisoning in addition to the well-known risks of thermal burns and denaturation. These are the leading cause of death, victims being generally found in the fire floor or in the one above. More than 5000 fire deaths are reported in the United States each year, of which 80% are related to smoke inhalation (2). In France, the Departmental Fire and Assistance Services reported, in 2006, 334012 interventions for fires, causing 11533 victims and 341 deaths (3). The annual incidence of poisoning by fire smoke is estimated at 20-40 per 100000 inhabitants in urban areas and the annual mortality 0.5-2 per 100000 inhabitants (4). However, despite all efforts of prevention, these figures have been sadly unchanged for the past 50 years. Residential fires often originate early morning, when people are deeply sleeping; and are closely correlated with vulnerable socio-economic conditions, smoking cigarettes and alcohol consumption by the victims themselves (5, 6).

Poisoning by inhalation of fire smoke combines, to varying degrees, a systemic neurological and cardiac involvement, due to anoxic gases and respiratory and ocular mucosal lesions, due to irritant gases found in smoke. Rescuers, firefighters and emergency physicians must be fully familiar with the management principles of these poisonings, including the diagnostic approach and methods of antidotes administration, because of the vital risks to the victims. The purpose of this overview is to present the latest international recommendations related to the subject.

1- MECHANISMS OF FIRE SMOKE TOXICITY

More than one hundred active ingredients with multiple toxicities are found in the fumes. The thermal degradation of materials produces heat, smoke and toxic gases; and combustion decreases the partial pressure of oxygen in the residential fire. Experimental studies conducted in the combustion chamber have revealed two types of materials thermal degradation: pyrolysis, namely the chemical decomposition of molecules under heat effect leading to flameless gas emission; and combustion corresponding to oxidation with heat and flames. Generated products depend on the nature of the initial fuel, the reached temperature and the richness of oxygen in the atmosphere.

During a fire in a confined space, reduction in fraction of inspired oxygen (FiO2) can occur in 1-2 minutes from 21% to 5.5%, with a parallel increase in the concentrations of CO and CO2, respectively at 5% and 10% (7). The central respiratory depression and neurological disorders appear at FiO2<17%, while at FiO2<10%, life becomes impossible.

Toxic gases produced during the thermal degradation of materials act either by cellular asphyxia and depression of the central nervous system, or by respiratory tract irritation (Table 1). In experimental models, high concentrations of these toxins caused death. However, lower concentrations are disabling, decelerating the leak and increasing the exposure time, and therefore the resulting morbidity and mortality. Incapacitating and irritating phenomena appear earlier than asphyxial phenomena, their effects being not only additive, but sometimes synergistic. The main toxic fumes in a fire are:

- **Carbon monoxide (CO):** It is constantly produced in fire due to incomplete combustion. The absorption of CO increases during hyperventilation due to the effort to escape the fire. CO attaches to hemoglobin and then limits oxygen transfer to tissues (Figure 3). A value of 40% of carboxyhemoglobin is incapacitating and a value of about 60% is deadly.

- **Carbon dioxide (CO2):** It is produced in large volumes during a fire. Even if CO2 is non-toxic by itself, low concentrations are sufficient to result in hyperventilation, facilitating the absorption of other toxic gases. For FiCO2 at 2%, ventilation minute increases by 50%, while it is doubled for FiCO2 at 5% and multiplied by 10 for FiCO2 at 10%. CO2 also causes respiratory acidosis, thus increasing the cerebral distribution of certain poisons, such as cyanide (CN) (8). The exact mechanism of these changes in tissue distribution is not unique, but corresponds to the increase in cerebral blood flow and to probable changes in the permeability of the blood-brain barrier.

- **Hydrogen cyanide (HCN):** During a residential fire, the combustion of many natural polymers (such as silk or wool) and synthetic polymers (such as polyurethane, poliamide, polycrionylitrile, and polystyrene) containing nitrogen, generates CN. The nature of the burning material determines the amount of generated CN. Thus, in an experimental combustion chamber, it is possible to obtain about 120, 200, 400 and 1500 ppm of HCN from 1g of foam rubber, wool, polyurethane or polycrionitrile, respectively (9,10). At the cellular level, CN binds to the mitochondrial cytochrome oxidase and blocks ATP production by the respiratory chain (Figure 1). CN can kill a human within minutes (Figure 2). The toxicity of HCN measured in monkeys depends on concentration in inspired air and duration of exposure (11). As with CO2, low concentrations of HCN in the inspired air (up to 80 ppm) lead to hyperventilation, which increases its own absorption and that of other toxic gases. The incapacitation is 20 times stronger than with CO. Exposure to 60 ppm of HCN for 30 minutes causes central nervous system depression, increased ventilation, but is free of cardiovascular effects. Depression becomes severe at 80-150 ppm HCN concentrations. At 196 ppm of HCN, the animal becomes unconscious in 2 minutes, but quickly awakens.

- **Soot:** They are microparticulate aerosols made of heavy hydrocarbons, polycyclic compounds of nitrogen and carbon. They are placed in the respiratory tract according to their size,
forming an adherent film on the bronchial epithelium. Soots are irritating and adsorbed on the surface, and thus can irritate mucous membranes with hypersecretion and scaling, which can cause bronchiolar obstruction. They are also the source of heat transfer, more than gases, therefore representing an important factor in burning both thermal and chemical airways.

- **Water vapor**: They lead to thermal damage at the bronchial tree level, because of their penetration depth and the amount of delivered heat.
- **Aldehydes**: The combustion of carbon chains generates many aldehydes, such as acrolein, formaldehyde, butyraldehyde and acetaldehyde. The acrolein and formaldehyde have a clear pulmonary toxicity, respectively 50 and 5 times as hydrochloric acid.
- **Derivatives of nitrogen**: Nitrogen oxides (NO and NO₂) and ammonia are released by polymers and /or nitrogen additives. Isocyanates are produced by the depolymerisation of polyurethanes. Amines are produced by the hydrolysis of isocyanates or volatilized from certain polymers (e.g.: epoxides, polyurethanes), which are the customary auxiliaries. Nitrogen peroxide reacts with hemoglobin to lead to methemoglobinemia.
- **Anhydrides**: Sulfur dioxide is released by the combustion of natural polymers (wool, silk, leather), while the acid anhydrides are resulting from certain polyesters or phthalate plasticizers.
- **Mineral acids** (hydrochloric, hydrofluoric, hydrobromic acids) carbon oxylhalides (phosgene (COCl₂): thermal degradation of materials containing chlorine (PVC, polymers fluorochlorohydrocarbons) produce hydrochloric acid. Various compounds are produced from Teflons®, depending on temperature and mode of combustion: hydrogen fluoride, carbonyl fluoride, tetrafluoroethylene, hexafluoropropylene, perfluoroisobutylene and hexafluoroethane. These compounds have a significant pulmonary toxicity and, in some cases, additional systemic toxicity.
- **Other gas with systemic toxicity**: In addition to highly irritating sulphur dioxide, other sulfur compounds are found, such as hydrogen sulphide (H₂S). A concentration of about 500 ppm causes coma and acute pulmonary edema. Flame retardants of plastics decrease burns risk but increase toxic risk, particularly convulsions by production of new compounds.

II - DIAGNOSTIC APPROACH

Smoke inhalation is the cause of two different toxic syndromes that may be present at varying degrees: syndrome of cellular deprivation of oxygen due to asphyxiating gases and syndrome of poisoning by toxic gases (12,13). For rescuers, it is essential to identify victims among the exposed people based on a simple clinical approach. The knowledge of cyanide toxidrome allows the administration of the antidote only to patients who need them. Thus, the presence of soot in the upper airways (nose, mouth and sputum) is a sensitive but nonspecific sign of smoke inhalation and therefore of poisoning from the two most dangerous gases, CO and CN. The absence of soot has an excellent negative predictive value.

II - 1 - Syndrome of cellular deprivation of oxygen

Anoxia is expressed by neurological, metabolic, and cardiovascular diseases (Table II). The spectrum of neurological involvement may be limited to headaches, dizziness, weakness, loss of consciousness or reach psychiatric disorders (agitation or confusion), coma, convulsions, and focal neurological deficit. Neurological manifestations can be associated with intoxication by CO, CN, or both. The decline in FiO₂ is also accompanied by the lack of physical co-ordination, depression of the central nervous system, and decrease in muscle strength. The initial loss of consciousness is always a sign of a significant systemic toxicity by asphyxiating gases. It also predicts the inhalation risk and respiratory complications. Central neurological disorders are constant in the case of cyanide poisoning. Collapse, shock or cardiac arrest is caused by exposure to poison gases, rarely involving CO alone, except for massive exposure (14). The combination of neurological disorder and hypotension should evoke poisoning by CN. The presence of “abnormal breathing”, whether polynea, wide ventilation, hypopnea or apnea, is also highly suggestive of cyanide poisoning.

For a fire victim without extended skin burns, lactacidemia is an excellent biological marker of cyanide poisoning. A concentration ≥ 10 μmol/L is a sensitive and specific indicator of intoxication

![Figure 1](image-url) - Mechanisms of toxicity of the two asphyxiating gases present in the fire smokes: Carbon monoxide binds to hemoglobin to give carboxyhemoglobin and thus reduces oxygen transport to the tissues. Cyanide inhibits mitochondrial cytochrome oxidase and blocks the oxidative phosphorylation responsible for ATP production: it causes anaerobic glycolysis and transformation of pyruvate to lactate.
defined by a CN concentration ≥ 40 μmol/L (15). Lactic acidosis only related to CO poisoning is rarely too severe (14). The formal confirmation of the diagnosis is then obtained secondarily by measuring blood CN: 40 μmol/L is considered the threshold for toxicity and 100 μmol/L threshold for lethality.

II - 2 - Syndrome of irritant gases-related toxicity

Mucosal lesions by gas released at the initial stage of the thermal degradation of materials in fire are formed in hours or few days (12,19). Eye irritation is manifested by conjunctivitis and corneal ulceration. It raises concerns for associated acute respiratory distress. Lesions of the tracheo-bronchial tree are manifested by acute respiratory failure that may exist immediately, independently from consciousness disorder. In the vast majority of cases, respiratory failure is still delayed a few hours from exposure. Dysphonia or auscultation abnormalities, such as rhonchi (snoring rhonchi) or sibilants (sharp hissing rhonchi) are evident in more than half of the victims. The presence of rhonchi is predictive of the occurrence of bronchopulmonary co-infection; usually associated with prolonged stay in the intensive care unit; in contrast, sibilants may be transitional and be cleared under bronchodilators (20).

Several types of injuries can co-exist in the respiratory tract, contributing to hypoxemia: laryngeal edema, bronchospasn, bronchial congestion by carbonaceous material, atelectasis, pulmonary edema of delayed onset... Tissue hypoxia is worsened by CO and/or CN poisoning. Cochineal red coloration of the skin in case of high carboxyhemoglobinemia hides an cyanosis. In addition, conventional pulse oximetry, unable to distinguish carboxyhemoglobin from oxyhemoglobin, can generate falsely reassuring SpO2.

Fire smokes cause chemical bronchial pneumonia and more rarely acute respiratory distress syndrome (ARDS). However, pulmonary infection by community germs (staphylococci, streptococci, anaerobic bacteria) is common during the first

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**Table I: Main gases and particles in fire smokes**

<table>
<thead>
<tr>
<th>Compounds causing toxicity by cell anoxia</th>
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<tbody>
<tr>
<td>Carbon monoxide (CO)</td>
</tr>
<tr>
<td>Hydrogen cyanide (HCN)</td>
</tr>
<tr>
<td>Carbon dioxide (CO2)</td>
</tr>
<tr>
<td>Nitrous monoxide (NO)</td>
</tr>
<tr>
<td>Anhydrous: sulphur andrid, hydrogen sulphide</td>
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</table>

<table>
<thead>
<tr>
<th>Compounds causing toxicity by mucosal irritation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soot (polycyclic microparticulate compound containing nitrogen and carbon)</td>
</tr>
<tr>
<td>Burning water vapor</td>
</tr>
<tr>
<td>Aldehydes: acrolein, formaldehyde, butyraldehyde et acetaldihyde</td>
</tr>
<tr>
<td>Nitrogen derivatives: nitrous oxide and ammonia, isocyanates and amines</td>
</tr>
<tr>
<td>Mineral acids: hydrochloric acid, hydrofluoric and hydrobromic</td>
</tr>
<tr>
<td>Carbon oxyhalides: phosgene</td>
</tr>
</tbody>
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**Table II: Differences in clinical presentation between victims of carbon monoxide and cyanide poisoning victims**

**Clinical presentation related to carbon monoxide poisoning**

- Neurological manifestations
  - Normal breathing (unless inhalation following a consciousness disorder)
  - Absence of hemodynamic failure
  - Low elevation of plasma lactate levels (~ 3 mmol/l)
  - Post-interval neurological syndrome
  - Anoxic sequela
  - Death

**Clinical presentation related to cyanide poisoning**

- Neurological manifestations
  - Normal breathing: polyneza, hyperpnea, hypopnea or apnea
  - Circulatory failure: arterial hypotension, collapsus, shock, cardiac arrest
  - Significant elevation of plasma lactate levels (≥10 mmol/l)
  - Anoxic sequela
  - Death
few days, with high incidence of aspiration pneumonia, especially in case of coma. This is also a significant condition explaining the need to prolong mechanical ventilation. If chest X-ray is part of the admission record, its prognostic value and specificity of abnormalities remain low. It can be completely normal, even though further development will be unfavorable. Poorly defined and disseminated alveolar-interstitial condensations are the most frequently observed abnormalities. Although abnormal, the images (bronchial thickening, pulmonary edema) do not allow to orient the differential diagnosis between cardiogenic pulmonary edema and lung injury, to support bacterial infection, or to provide adequate prognosis. In addition, hypoxia is not correlated with the extent of X-ray abnormalities. The presence of soot in the nasal or oropharyngeal cavity cannot predict the distal lung damage, but is associated with prolonged mechanical ventilation (21). The systematic implementation of bronchial fibroscopy has been proposed for diagnostic, prognostic, and therapeutic purposes. Some teams offer such a strategy to immediately confirm exposure to fumes and classify lesions. One of the simplest classifications of ENT and tracheo-bronchial injuries is completed in three stages: stage 1 (edema, hyperemia, and hypersecretion), stage 2 (mucous bullous detachment, superficial mucosal ulcers, and exudates) and stage 3 (deep mucosal ulcerations and necrosis). For non-burnt patients, even if bronchial injuries may precede the appearance of arterial blood gases or radiological anomalies, it seems difficult to assign a predictive value. In addition, the appearance of the mucosa may be falsely reassuring by the paleness in patients with collapse. Conversely, in case of burnt patients who have inhaled toxic gases, fiberoptic endoscopy may facilitate intubation in the presence of severe injuries in upper airways, allow bronchial clearance removing mucous debris and soot secretions difficult to mobilize, and predict the risk of death from ARDS (22,23). Pro-inflammatory profile of cytokines measured in plasma or bronchoalveolar lavage fluid in these patients reflects the severity of the lesions of broncho-pulmonary inhalation and is closely correlated with final prognosis (23,24). However, a strong initial hypo-immune response to heat stress appears to be associated with a fatal outcome (25).

III - MEDICAL MANAGEMENT

The main goal when treating a smoke inhalation victim is to ensure satisfactory oxygenation (26,27). After having secured airways, oxygen is delivered to the patient as soon as the prehospital stage and, if necessary, tracheal intubation is performed in the presence of respiratory or neurological failure. Finding stridor should draw attention to the risk of rapidly progressing obstruction of the airways. In practice, about 50% of inhalation victims suffering from burns should be intubated. Tracheal intubation should be early in case of dysphonia and dyspnea, even though it is not recommended as prophylaxis. Any delay and/or secondary accidental extubation may lead to death. In case of massive laryngeal edema, a tracheotomy may be necessary immediately.

The treatment of acute respiratory failure due to ARDS usually caused by irritating gas-related bronchial and alveolar injuries is based on the principle of protective ventilation to minimize the risk of barotrauma maintaining a plateau pressure <30 cmH2O. Less conventional techniques of ventilation or oxygenation (high frequency ventilation, percussive ventilation, and extracorporeal membrane oxygenation) have been proposed in refractory cases; however, no controlled studies have been performed in humans in the setting of smoke inhalation, even though hopes to reduce mortality really exist (28).

Curiously, an experimental model seems to suggest a less favorable evolution with Airway Pressure Release Ventilation (APRV) than with conventional ventilation (29). Administration of inhaled nitric oxide has not been specifically evaluated in this indication. It should be noted that fumes are very rich in nitrous monoxide, while its role is not precisely known among fire victims (30).

Effectiveness of β2-agonists by inhalation route has not been specifically evaluated; however, they be immediately administered to treat bronchospasm and improve ventilatory mechanics (31). Inhaled epinephrine is often used in practice: interestingly, a recent experimental study seems to show an interest in reducing hyperemia, mucusal edema, and deleterious bronchial reactivity after smoke inhalation-related acute lung injury (32). Administration of inhaled antioxidants like N-acetylcysteinne or inhaled anticoagulants like heparin is widely practiced (31). Additionally, like γ-tocopherol, several other therapies have been proposed to reduce the damage of ARDS on experimental studies basis (33). Innovative therapies are currently being tested (Table III). Conversely, the use of corticosteroids has not proven effective neither in animal models nor in clinical studies (34). Their administration in burnt victims with inhalation injuries increases even the risk of infection and mortality. However, their prescription can be discussed case by case when bronchospasm refractory to conventional therapy will complicate lesions inhalation. Prescribing prophylactic antibiotics can be harmful. The antibiotic therapy is indicated only for documented infections and will be guided by the results of microbiological samples.

III -1- Treatment of carbon monoxide poisoning associated with smoke inhalation

A fire victim shall receive isobaric oxygen upon discovery (26,27). There is no randomized controlled trial evaluating the value of hyperbaric oxygenation (HBO) on the final outcome of smoke inhalation victims. Thus, although some authors report a possible interest in prophylactic HBO on the level of progression of smoke inhalation-related pulmonary inflammatory injuries (35), the decision to use it should depend only on the suspicion of associated CO poisoning (36). Moreover, HBO does not affect blood CN concentrations, and therefore the need to use a specific treatment (37). Regarding the consequences of CO poisoning, current data show that victims who exhibited no neurological manifestation, even though minor, and who are stable from a hemodynamic point of view, have a very low risk of developing subsequent neurologic sequelae. These patients can be treated with isobaric oxygen therapy. In contrast, in the presence of consciousness disorders, HBO treatment is preferable, if immediately available. Pregnant women, even asymptomatic, should benefit, to prevent fetal hypoxia. Children should also benefit, even if the data regarding the fate of children poisoned by CO fumes are limited (38). There is no consensus on the minimum rate of COHb that imposes an HBOT treatment. Two pitfalls should be avoided in clinical practice: on the one hand, ignorance of clinical signs at the fire scene or upon admission to the hospital, leading to the abstention of hyperbaric therapy, and on the other, in case of HBO unavailability, a worsening of the clinical situation caused by the transfer of an unstable patient because of associated injuries (burns, trauma).
Treatment of cyanide poisoning associated to smoke inhalation

Many antidotes are available to treat cyanide poisoning (12,25,27,39). Their mechanism of action are well known, but no clinical study has compared their effectiveness. Methemoglobinizing agents (sodium nitrite, amyl nitrite and 4-dimethylaminophenol) are effective, with the strict condition of inducing 20-30% methemoglobinemia. They are hence totally not recommended in a fire context due to their related reduced blood capacity to carry oxygen and vasodilatation that sometimes brutally occurs. Thus, experimentally, these agents have been shown to increase mortality in animals treated for poisoning by mixed CO and CN (40). Sodium thiosulfate increases the speed of CN physiological transformation into thiocyanate by rhodanese of Lang also called hepatic thiosulfate sulfurtransferase: it is effective and well tolerated, but its action is too slow compared to the hyperacute time-course of fire poisoning victims.

EDTA dicobaltite is very effective experimentally, but its bad hemodynamic tolerance and side-effects (vomiting, urticaria, anaphylactoid reactions, and ventricular arrhythmia) are limiting factors. Hydroxocobalamin or vitamin B12 is a large molecule containing a cobalt atom (Figure 3). It acts rapidly by neutralizing the CN without compromising tissue oxygenation (12,39,41). Due to its high affinity for CN, it is able to redistribute it from its target (mitochondrial cytochrome oxidase) into the plasma compartment to form cyanocobalamin, a stable and non-toxic molecule, in a mole-to-mole combination. Hydroxocobalamin features a remarkable tolerance that has been demonstrated not only in patients with suspected CN poisoning by ingestion but also among fire victims having inhaled fumes and being or not intoxicated by CN (42,43). Even in the absence of randomized clinical trials, its effectiveness is now recognized to treat cyanide poisoning related to fire smoke inhalation (41). Moreover, its efficacy and excellent tolerability in children or pregnant women have been assessed in several published clinical cases (44,45). But in the absence of more significant data, its current use should be limited to cases where the benefits go beyond the expected risks. Based on these studies, the European Society for Emergency Medicine (46) and the Australian Resuscitation Council (47) have recommended the use of hydroxocobalamin as first-line antidote at the fire scene itself, in any patient with suggestive features of cyanide poisoning before further confirmation or exclusion based on toxicological analysis. 4A and 4B figures show the European guidelines for the pre- and intra-hospital management of fire smoke inhalation victims. During a fire, cyanide poisoning is highly probable in the presence of soot in the upper airways and neurological disorders (loss of consciousness particularly) with one of the following three signs: cardiovascular collapse, polyphonia or bradypnea and/or plasma lactate concentration ≥ 10 mmol/l (Table IV). To clarify pre-hospital management (Figure 4A), European recommendations have focused on the persistence of consciousness disorders despite oxygenation with 100% FiO2 for few minutes, a presentation highly suggesting cyanide poisoning. In these patients and due to its safety, administration of hydroxocobalamin is fully recommended (46). For adults, the initial dose is 5 g and 70 mg/kg for children, without exceeding a maximum of 5 g. Intravenous infusion is mandatory (Figure 3). Treatment effectiveness is evaluated by the improvement in hemodynamic status with catecolamine weaning and lactic acidosis correction. Depending on the severity of poisoning and clinical response, a second dose may be infused in adults (5 g) as in children (without exceeding a maximum of 5 g). This is recommended in case of initial cardiac arrest, persistent shock or absence of fast lactate normalization. After administration of hydroxocobalamin, it is possible to confirm the diagnosis of CN poisoning by measuring the amount of cyanocobalamin excreted in the urine during the first 3 days (48,49). Hydroxocobalamin side-effects are minimal: reversible pink color of the skin, mucous membranes, and urine, reversible facial edema, as well as a transient and usually asymptomatic increase in blood pressure (41). Note, however, the possibility of interference with some laboratory tests like carboxyhemoglobin measurement (50), as well as alarms of some extracorporeal renal replacement devices, which must be recalibrated (51-53). Sodium thiosulfate is recommended in the hospital in case of persistent hyperlactatemia due to cyanide poisoning despite the administration of 10 g of hydroxocobalamin (46). However, in case of simultaneous infusion of sodium thiosulfate and hydroxocobalamin, two separate venous lines should be used because these two molecules are chemically incompatible (47).

IV- COMPLICATIONS AND SEQUELAE

Hospital mortality remains high (30-50%), when extended skin burns (≥ 10% body surface area) exist. Among non-burnt victims, mortality is lower (<10%). Smoke inhalation is associated with either ARDS or with irreversible neurological anoxic injuries. Mortality of fire victims found in cardiac arrest exceeds 80%. The few victims who survive may then suffer from chronic post-anoxic encephalopathy or extremely incapacitating neurological sequela. Barotraumatic injuries of mechanical ventilation and hospital-acquired pulmonary infections are the cause of early respiratory
airways dysfunction syndrome), bronchiolitis obliterans, and bronchiectasis (54). Despite very short exposure times to CO, smoke inhalation may represent a cause of post-interval syndrome whose frequency of occurrence has not been established and which may result in potentially serious manifestations including abnormal movements, cortical blindness, and akinetic mutism. Cyanide poisoning may also leave central nervous system sequelae in approximately 20% of survivors (55). Interpretation of brain imaging then requires special expertise, due to similarities and overlapping between CO- and CN-related brain injuries (56). Smoke inhalation may finally lead to irreversible cognitive or emotional disturbances, causing disruption of social and professional life. It is therefore a typical example of poisoning-related chronic disease, which may sometimes be excessively disabling.

**CONCLUSIONS**

Fire smokes are responsible for pulmonary and systemic toxicity resulting in the majority of immediate and delayed deaths. CO and CN are the two main cell-asphyxiating and poisonous gases, with potential synergistic toxicities. Oxygenation, including by the route of intubation and mechanical ventilation should always be prompt. In the presence of signs suggestive of cyanide poisoning, an efficient antidote should be immediately administered on the fire scene. Because of its safety and effectiveness, both clearly assessed on relatively large cohorts of patients, hydroxocobalamin is considered to date as the first-line anti-cyanide antidote. Finally, smoke inhalation remains a major cause not only of acute life-threatening organ failures, but also of chronic diseases altering the final functional outcome by possible respiratory and neurological sequelae.

Table IV – Indications and methods of hydroxocobalamin administration

<table>
<thead>
<tr>
<th>Indications</th>
</tr>
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<tbody>
<tr>
<td>1. Soot around the mouth, nose and/or pharyngeal and/or sputum</td>
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<tr>
<td>2. Neurological disorders (including loss of consciousness)</td>
</tr>
<tr>
<td>3. One of the following signs: respiratory abnormalities (bradypnea or polyplea), hypotension, shock, cardiac arrest or lactic acidosis (plasma lactate concentration ≥ 10 mmol/l)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methods of administration</th>
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<tbody>
<tr>
<td>Reconstitute the 5 g vial with 200 ml of 0.9% NaCl</td>
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<tr>
<td>Turn the bottle upside down several times without stirring for 1 minute</td>
</tr>
<tr>
<td>Connect the infusion set provided in the kit</td>
</tr>
<tr>
<td>Administer the drug by IV infusion during 15 min</td>
</tr>
</tbody>
</table>

![Figure 3 - Hydroxocobalamin: chemical structure and presentation of the treatment together with its infusion set](image-url)
Figure 4A - The European recommendations for the pre-hospital management of fire smoke inhalation victims [adapted from Anseeuw et al. (46)]

* If cardiac arrest, give 10g of Hydroxocobalamin
** If several victims, begin with 2.5g and complete to 5g

Figure 4B - The European guidelines for hospital care of fire smoke inhalation victims [adapted from Anseeuw et al. (46)]
REFERENCES