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Acute clinical manifestations in toxic smoke inhalation victims: systematic review of observational studies

Manifestações clínicas agudas em vítimas de inalação de fumaça tóxica: revisão sistemática de estudos observacionais

Manifestaciones clínicas agudas en víctimas de inhalación de humos: revisión sistemática de estudios observacionales

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Abstract

Introduction: Lung injuries from toxic smoke inhalation are the main causes of death in fire victims; however, information regarding the acute effects on the respiratory system after smoke inhalation and its constituents in closed environments are still scarce in literature. **Objective**: To investigate the acute clinical manifestations observed in victims of smoke inhalation during enclosed-space fires by means of systematic review.

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Methods: A systematic search was conducted in the following databases: MEDLINE (via PubMed), Lilacs, Scopus and Web of Science. There were no applied *restrictions* in terms of the *publication date*. In addition, a manual search was performed on the references of published studies. Observational studies assessing the prevalence of acute clinical manifestations in victims of toxic smoke inhalation in closed environments were included. **Results**: Of the 4,603 articles identified, eight were included, comprising a total of 233 patients. The signs and symptoms were identified and ranked according to frequency. Dyspnea (58.80%, six studies), carbonaceous sputum (54.51%, four studies), hoarseness (39.91%, three studies), wheezing (34.33%, five studies) and sore throat (33.90%, two studies) were the most frequent acute clinical manifestations of smoke inhalation. Besides these, chest pain and pulmonary edema were observed, respectively in 13.30%, 5.15% of the studies. **Conclusion**: The results suggest that dyspnea, carbonaceous sputum, hoarseness, wheezing and sore throat were the most frequent acute clinical manifestations in victims of smoke inhalation. Further studies of a higher level of evidence and greater methodological rigor are required.

Keywords*:* Smoke Inhalation Injury. Hydrogen Cyanide. Carbon Monoxide. Lung Injury.

Resumo

Introdução: *As lesões pulmonares decorrentes da inalação de fumaça tóxica são as principais causas de morte em vítimas de incêndio; no entanto, informações a respeito das repercussões agudas no sistema respiratório decorrentes da inalação de fumaça e seus constituintes em ambientes fechados ainda são escassas na literatura.* ***Objetivo****: Investigar as manifestações clínicas agudas observadas em vítimas de inalação de fumaça tóxica em ambientes fechados através de uma revisão sistemática.* ***Métodos****: Uma pesquisa sistemática foi realizada nas seguintes bases de dados: MEDLINE (via PubMed), Lilacs, Scopus e Web of Science. Não houve restrições quanto ao ano de publicação. Além disso, realizou-se uma pesquisa em referências de estudos publicados. Foram incluídos estudos observacionais que avaliaram a prevalência das manifestações clínicas agudas em vítimas de inalação de fumaça tóxica em ambientes fechados.* ***Resultados****: Dos 4.603 artigos encontrados, oito foram incluídos, compreendendo um total de 233 pacientes. Os sinais e sintomas foram identificados e classificados de acordo com a frequência com que apareceram nos estudos incluídos. Dispneia (58,80%, seis estudos), escarro carbonáceo (54,51%, quatro estudos), disfonia (39,91%, três estudos), sibilância (34,33%, cinco estudos) e dor de garganta (33,90%, dois estudos) foram as manifestações clínicas agudas mais frequentes de inalação de fumaça. Além disso, dor torácica e edema pulmonar foram observados, respectivamente em 13,30% e 5,15% dos estudos.* ***Conclusão****: Os resultados sugerem que dispneia, escarro carbonáceo, disfonia, sibilância e dor de garganta foram as manifestações clínicas agudas mais frequentes nas vítimas de inalação de fumaça tóxica. São necessários novos estudos com alto nível de evidência e melhor rigor metodológico.*

Palavras-chave: *Lesão por Inalação de Fumaça. Cianeto de Hidrogênio. Monóxido de Carbono. Lesão Pulmonar.*

Resumen

Introducción*: Las lesiones pulmonares producidas por la inhalación de humo son las principales causas de muerte entre las víctimas de fuego, sin embargo, informaciones con respeto de las repercusiones agudas en el sistema respiratorio derivadas de la inhalación de humo y sus constituyentes en ambientes cerrados siguen escasas en la literatura.* ***Objetivo****: Investigar las manifestaciones clínicas agudas observadas en víctimas de inhalación de humo en ambientes cerrados a través de una revisión sistemática.* ***Métodos****: Una pesquisa sistemática fue realizada en las siguientes bases de datos: MEDLINE (vía PubMed), Lilacs, Scopus y Web of Science. No hubo restricciones con relación al año de publicación. Además, se realizó una pesquisa en referencias de estudios publicados. Fueron incluidos estudios observacionales que evaluaron la prevalencia de las manifestaciones clínicas agudas en víctimas de inhalación de humo tóxico en ambientes cerrados.* ***Resultados****: De los 4.603 artículos encontrados, ocho fueron incluidos, comprendiendo un total de 233 pacientes. Los signos y síntomas fueron identificados y clasificados de acuerdo con la frecuencia con que aparecieron en los estudios incluidos. Disnea (58,80%, seis estudios), esputo*

carbonáceo (54,51%, cuatro estudios), disfonía (39,91%, tres estudios), sibilancia (34,33%, cinco estudios) y dolor de garganta (33,90%, de los estudios) han sido las manifestaciones clínicas agudas más frecuentes de la inhalación de humo. Además, dolor torácico y edema pulmonar han sido observados, respectivamente en 13,30% y 5,15% de los estudios. ***Conclusión*****:** *Los resultados sugieren que la disnea, esputo carbonáceo, disfonía y dolor de garganta fueron las manifestaciones clínicas más frecuentes en las víctimas de inhalación de humo tóxico. Son necesarios nuevos estudios con alto nivel de evidencia y mejor rigor metodológico.*

Palabras clave*: Lesión por Inhalación de Humo. Cianuro de Hidrógeno. Monóxido de Carbono. Lesión Pulmonar.*

Introduction[1]

On January 27, 2013, Brazil experienced one of the biggest tragedies involving a fire in a closed environment, which killed 242 people and ended up with another one thousand injured. The fire at the Kiss nightclub in the city of Santa Maria, State of Rio Grande do Sul, in Southern Brazil, is worldwide considered the second biggest fire occurred in a nightclub, only exceeded by the Cocoanut Grove nightclub fire in Boston, Massachusetts, USA, in November 1942. Kiss nightclub's was the second highest death toll due to fire in Brazilian history; the first one happened in 1961 in the city of Niterói, State of Rio de Janeiro, at the Gran Circus Norte-Americano, which killed 503 people [1].

Smoke inhalation and its lung injury consequences are considered a leading cause of immediate death in fire victims [2, 3], and represent also a majority causes of mortality and morbidity related to exposure to smoke from fire [4].

In a close environment, it is impossible to predict the pathophysiological interactions of all smoke toxins, especially if we consider the wide variety of pyrolysis components [2]. In this sense, hydrogen cyanide (HCN) and carbon monoxide (CO) gases are commonly found at elevated concentrations in fire smoke and are associated with a high incidence of immediate death, severe morbidity and mortality [5-7].

In this context, fire-related inhalation injury can result from direct local thermal and chemical exposures, immune responses to these factors, systemic effects of inhaled toxins, accrual of endobronchial debris, and secondary infection. The effect for individual patients is complex and unpredictable [8].

Individuals who are accidentally exposed to toxic gases, as HCN and CO, usually present vague and nonspecific symptoms [9]. In this sense, classically, the diagnosis of inhalation injury was subjective and made based on clinical findings [10]. Despite the fact, according to Sheridan [8], the specific therapeutic interventions remain ineffective, the individual risk of death remains difficult to quantify, and the long-term implications for survivors remain ill-defined.

Previous studies addressed the long-term effects of smoke inhalation on the respiratory system. These studies demonstrated a lung function decline and chronic respiratory symptoms [9, 11, 12]; however, studies evaluating initial clinical manifestations in the early phase of patients with smoke inhalation injuries are still scarce.

Based on this, we aimed to carry out, for the first time, a systematic review of the literature to investigate the acute clinical manifestations on the respiratory system observed in victims of smoke inhalation during enclosed-space fires.

Methods

This systematic review was performed following the recommendations proposed by Preferred Reporting Items for Systematic Review and Meta-analyses: The PRISMA Statement [13]. The protocol of systematic review was prospectively registered at International Prospective Register of Systematic Review database (PROSPERO) under the identification CRD42016042728.

Sources and search strategy

The investigators, who received formal training in systematic review, performed all searches. A systematic

[1] **Clinical Trial Registration Information —** URL: http://www.crd.york.ac.uk/PROSPERO. Unique identifier: CRD42016042728.

search was performed in the following electronic databases: MEDLINE (accessed via PubMed), Lilacs, Scopus, and Web of Science.

The search strategy used in PubMed is shown in Table 1. There were no applied *restrictions* in terms of the *publication date.* Articles in Portuguese, Spanish or English were included. A manual search was performed, but no unpublished study or conference abstract fulfilled the inclusion criteria. Thus, there was no need to contact authors for further information or to handle unpublished abstracts.

Table 1 - Search strategy used in PubMed

#1	"Inhalation Exposure", "Exposure, Inhalation", "Exposures, Inhalation", "Inhalation Exposures", "Smoke Inhalation Injury", "Inhalation Injury, Smoke", "Injury, Smoke Inhalation", "Inhalation Injuries, Smoke", "Injuries, Smoke Inhalation", "Smoke Inhalation Injuries", "Burns, Inhalation", "Inhalation Burns", "Burn, Inhalation", "Inhalation Burn"	Smoke Inhalation
#2	"Hydrogen Cyanide", "Cyanide, Hydrogen", "Hydrocyanic Acid", "Acid, Hydrocyanic", "Zyklon B", "Carbon Monoxide", "Monoxide, Carbon", "Carbon Monoxide Poisoning", "Poisoning, Carbon Monoxide", "Carbon Monoxide Poisonings", "Monoxide Poisoning, Carbon", "Monoxide Poisonings, Carbon", "Poisonings, Carbon Monoxide", "Poisoning, Illuminating Gas", "Gas Poisoning, Illuminating", "Gas Poisonings, Illuminating", "Illuminating Gas Poisonings", "Poisonings, Illuminating Gas", "Illuminating Gas Poisoning", "cyanide poisoning"	Toxic gases
#3	"Lung Injury", "Injuries, Lung", "Injury, Lung", "Pulmonary Injury", "Injuries, Pulmonary", "Injury, Pulmonary", "Pulmonary Injuries", "Lung Injuries", "Chronic Lung Injury", "Chronic Lung Injuries", "Lung Injuries, Chronic", "Lung Injury, Chronic", "Pulmonary Complications", "Acute Lung Injury", "Acute Lung Injuries", "Lung Injuries, Acute", "Lung Injury, Acute"	Lung injury
#4	#1 OR #2	
#5	#4 AND #3	

Eligibility criteria

This review included observational studies (case study and case series) assessing the prevalence of acute clinical manifestations (in the first 24 hours) in victims of toxic smoke inhalation in closed environments. Experimental studies, postmortem analysis, comparison among diagnostic methods, comparison of preexisting chronic conditions, studies that have addressed long-term clinical manifestations or about the management of patients with smoke inhalation were excluded.

Data extraction

Two reviewers independently extracted the data from the eligible studies by using a standardized data extraction form. The following data were extracted: authors; year of publication; country of the research; study design; patient characteristics (demographics, sample size); fire location and acute clinical manifestations (clinical presentation, chest examination and radiologic findings).

Results

Description of studies

Of the 4,603 studies identified in the search, eight matched the eligibility criteria, yielding a total of 233 patients. Figure 1 shows the flowchart of the studies included in this review and Table 2 summarizes their characteristics.

Table 2 - Characteristics of the included studies

(to be continued)

Author, year	Country	Type of study	Patient characteristics	Initial clinical manifestations
McArdle and Finlay, 1975 [14]	Scotland	Case study	n = 2 (M) Age = 27 and 58 years Household fire	- RF: pulmonary edema
Putman et al., 1977 [15]	Unites States of America	Case series	n = 21 (M = 11; F = 10) Age = 2-81 years Household fire	- Dyspnea, carbonaceous sputum, and hoarseness. - PE: rhonchi, rales and wheezing. - RF: focal infiltrates and pulmonary edema.
Lee and O'Connell, 1988 [16]	Ireland	Case series	n = 45 Nightclub fire	- Dyspnea. - RF: subglottic edema, bronchial wall thickening, pulmonary edema and consolidation.
Stenton et al., 1988 [17]	England	Case study	n = 2 (M) Age = 30 years Household fire	- Dyspnea, dry cough, chest pain and tachypnea. - PE: wheezing. - RF: pneumomediastinum.

(Conclusion)

Hantson et al., 1997 [18]	France	Case series	n = 64 (M = 36; F = 28) Age = 47.3 years (range 20-94 years) Household fire	- Hoarseness, carbonaceous sputum. - PE: rhonchi, rales and wheezing.
Cha et al., 2007 [19]	Republic of Korea	Case series	n = 96 (M = 43; F = 53) Age = 35.2 ± 2.56 years Subway station fire	- Cough, dyspnea, sore throat, carbonaceous sputum, hoarseness, and chest pain. - PE: wheezing and stridor
Dinh and Rosini, 2014 [20]	Unites States of America	Case study	n = 1 (F) Age = 50 years Household fire	- Dyspnea, tachycardia, productive cough and nausea.
Tyagi et al., 2015 [21]	India	Case study	n = 2 (M) Age: 21 and 24 years Submarine fire	- Dyspnea, carbonaceous sputum, chest pain, tachycardia, tachypnea, desaturation and sore throat. - PE: rales and wheezing. - RF: acute bilateral airspace opacification. - CT: ground glass opacities and patchy consolidation.

Note: RF = radiologic findings; PE = physical examination; M = male(s); F = female(s); CT = computed tomography.

According to their study design, four of the studies were case series [15, 16, 18, 19] and the other studies were case studies [14, 17, 20, 21]. Most selected studies described two cases [14, 17, 21] and one of them only one case study [20].

The most common acute clinical manifestations in victims of toxic smoke inhalation in closed environments were dyspnea (n = 137, 58.80%) [15-17, 19-21], carbonaceous sputum (n = 127, 54.51%) [15, 18, 19, 21], hoarseness (n = 93, 39.91%) [15, 18, 19], wheezing (n = 80, 34.33%) [15, 17-19, 21] and sore throat (n = 79, 33.90%) [19, 21]. Beside this, pulmonary edema and chest pain were reported with prevalence rates of 5.15% [14-16] and 13.30% [17, 19, 21], respectively. The lowest prevalence found in the included studies was of 5.15% and the highest was 58.80%.

The fire location differed among the studies. The study conducted by Cha et al. [19] reported a fire accident in a subway station in the city of Daegu, South Korea; another study [21] described a fire accident onboard India Naval Submarine; the study conducted by Lee and O'Connell [16] reported an accident in a nightclub in the city of Dublin, Ireland. Another five studies [14, 15, 17, 18, 20] described a household fire accident.

The age of the patients with inhalation injuries ranged from 2 years to 81 years. Considering the gender of the patients, there was male predominance in five studies [14, 15, 17, 18, 21]. One study did not report the gender of the sample [16].

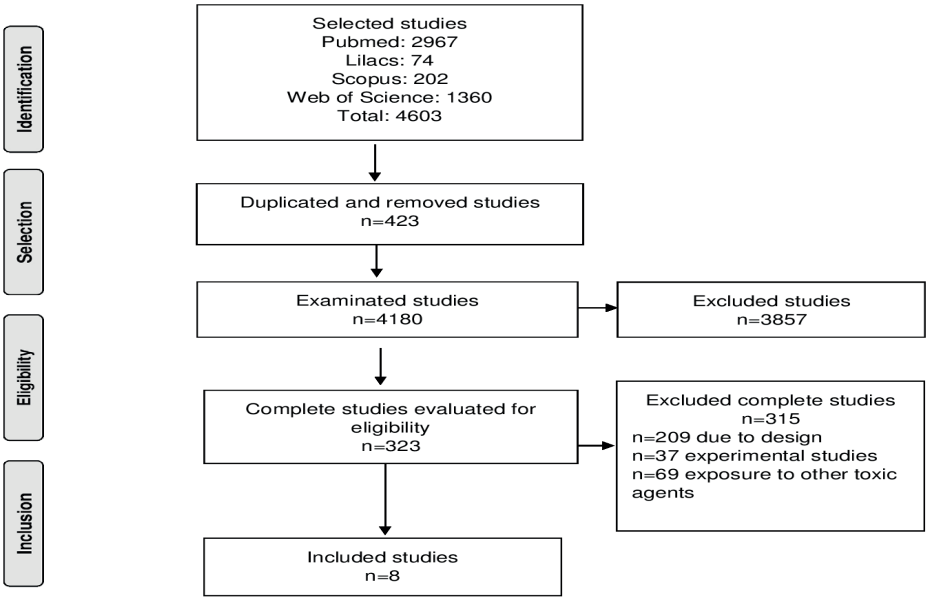

Figure 1 - Flowchart for the studies identified for analysis

Discussion

To the best of our knowledge, this is the first systematic review to describe the acute clinical manifestations observed in victims of smoke inhalation during enclosed-space fires. The most common acute clinical manifestations were dyspnea, carbonaceous sputum, hoarseness, wheezing and sore throat. Besides this, pulmonary edema and chest pain have also been reported. Because of the heterogeneity between studies, it was not possible to perform a meta-analysis.

In fires, oxygen is either consumed by combustion or displaced by other gases and its concentration reduction in ambient results in decreased oxygen delivery and it may contribute to asphyxiation and mortality. In this context, the low arterial partial pressure of oxygen and the low pH of acidosis are sensed by chemoreceptors of the carotid bodies and neural signals are transmitted to centers of the brain stem, where they are integrated and result in the sensation of dyspnea [22]. In addition, dyspnea may occur due to various reasons that vary depending on the gas that was inhaled as well as due to the decreased ambient oxygen concentration [23], the decrease of oxygen supply through binding to hemoglobin [24] or by the inhibition of cellular oxygenation, which causes tissue anoxia by inhibition of cytochrome oxidase enzymes [25]. Of the eight included studies, six presented dyspnea [15-17, 19-21]. Only two did not demonstrate this manifestation [14, 18]. We believe that it may have occurred because the study conducted by McArdle and Finlay [14] was a two-case study and consequently, has less chance to present this manifestation. Moreover, the study conducted by Hantson et al. [18] was a retrospective study, which may have risk of selection bias and consequently justify the absence of findings related to this manifestation. Besides this, from the 64 subjects included in their analyses [18], loss of consciousness was presented in 21 subjects and 18 of these were intubated at the scene of the fire. Based on the above, we suppose the lack of this manifestation may be a bias considering that it is unlikely that from 64 subjects, no one has presented this symptom, which was observed in 137 subjects of the other included studies.

Regarding other acute clinical manifestation, hoarseness was observed in 93 subjects of the 233 included in this systematic review. This finding is relevant because the presence of hoarseness indicates the necessity of mechanical ventilation and prolonged ICU stay [18]. On the other hand, the presence of carbonaceous sputum, the second most common found manifestation, does not predict the severity of airway injury [26]. An overall synthesis of the other included studies has not been possible, because only the frequency of the clinical manifestations was presented. Also, they have poor generalizability due to variations in confounding effect modifiers and different selection biases operating at specialist treatment centers.

In relation to the male predominance in the present systematic review, it is known that this group is more prone to be involved in accidents that result in death [27, 28]. Earlier studies also demonstrated a greater male involvement among victims of smoke inhalation during enclosed-space fires [29-32]. On the other hand, regarding the fire location, most studies described a household fire accident [14, 15, 17, 18, 20]. This finding is consistent with what was previously reported in two studies, which showed that the majority of fire accidents occur in a domestic environment [33, 34].

It should also be considered that the severity of inhalation injuries can be influenced by the component materials of the structures. Due to the increasing use of synthetic materials in interior furnishings and building construction, the toxic constituents of modern structural fires began to be associated with a higher degree of toxicity, potentially resulting in more severe inhalation injuries and worse clinical outcomes [35, 36]. The different materials and components of constructions used in the past may be a potential reason for the distinct clinical manifestations found in the present study, since from the eight included studies, five of them are older studies [14-16, 17,18].

In relation to radiological findings, the presence of pulmonary infiltrates at initial evaluation has been indicated as a marker of severe injury and a poor prognosis [14]. Lee and O'Connell [16] demonstrated that the initial chest radiography is an important predictor of significant smoke inhalation injuries, enabling the selection of patients likely to need ventilatory support.

Earlier studies have explained the role of early recognition and prompt management in the presence of smoke inhalation injury [37, 38]. Another study included [20] in this systematic review also demonstrated that early identification and intervention are vital in cyanide toxicity, and that empire antidotal treatment should not be delayed. Furthermore, it is also known that pulmonary effects of smoke inhalation injury may vary from cough and dyspnea, within minutes to hours of exposure [39] to acute lung injury, acute respiratory distress syndrome [40] and long-term pulmonary dysfunction [39].

Although this is the first systematic review to describe the acute clinical manifestations observed in victims of toxic smoke inhalation during enclosed-space fires,

based on a comprehensive and systematic bibliographic search, that employed an explicit methodology and reproducible eligibility criteria, unrestricted by date or language and performed independently by two reviewers, some limitations merit discussion. First, because of the methodological heterogeneity between studies, it was not possible to perform a meta-analysis. Second, the impossibility of methodological assessment using the Newcastle-Ottawa scale. This scale was designed to evaluate the quality of case-control and cohort studies, although in the present study, four of the studies were case series and the other studies were case studies. Finally, deficits in the design and different ways of reporting data in the included studies. Therefore, it is possible that this systematic review is subject to bias through the inclusion of low-quality studies.

In this way, the present systematic review allows the conclusion that dyspnea, carbonaceous sputum, hoarseness, wheezing, and sore throat were the most frequent acute clinical manifestations of smoke inhalation. These findings have potential clinical implications on early identification of signs and symptoms, and improvement of early physiotherapy intervention for patients with inhalation injury, which in turn may lead to increased survival and reduce the risk of mortality and treatment of long-term effects of smoke inhalation.

Conclusion

Dyspnea, carbonaceous sputum, hoarseness, wheezing and sore throat were the most frequent acute clinical manifestations observed in victims of toxic smoke inhalation in closed environments. Further studies of higher level of evidence and greater methodological rigor are required.

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