Original Article

Delayed onset pulmonary edema following toxic smoke inhalation; a systematic review

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Abstract

Background: *Fire smoke inhalation cause a wide range of symptoms immediately or after a relatively asymptomatic period. In this review, we will focus on delayed onset pulmonary edema (DOPE); the incidence and duration of potential delay. As the symptoms may not present immediately, seemingly healthy patients could be inadvertently be sent home. Therefore, many authors recommend observation for 6-24 hours depending on the extent of inhalation injury.*

Methods: *A systematic literature search in Embase, Medline, and Cochrane library was performed on 14 April 2016. All studies describing smoke exposure and delayed pulmonary edema were included. Additional relevant studies were identified snowballing based on included studies.*

Results: *We included seven studies, with a total of 135 patients, describing pulmonary edema. Symptoms generally developed after a relatively asymptomatic period (up to 36 hours post-injury) until mechanical ventilation was needed. However, pulmonary edema developing after 36 hours was most likely due to other factors related to burn injury (excessive intravenous fluids, de novo heart failure, infection or problems related to intubation).*

Conclusion: *Delayed onset pulmonary edema can develop as late as 36 hours postinjury after a relatively uneventful phase. But it would have been rare to have been completely asymptomatic before developing pulmonary edema.*

Introduction

Smoke inhalation and respiratory failure can be seen with or without burn injury and is the main cause of mortality in burn victims.[1, 2] Inhalation injury can be divided into three types of lesions, thermal injuries (causing upper airway obstruction due to edema and sloughing of the epithelium presenting as stridor or obstruction), chemical injuries (to the subglottic airways due to chemicals and irritants in the smoke such as soot, Cl_2, HCl, NH_3, HF, SO_2, NO_x, $COCl_2$, H_2S, aldehydes, and aromatic hydrocarbons leading to inflammation and irritation of the upper and lower airways, bronchoconstriction, bronchorrhea, sloughing, casts and obstruction of lower airways, or pulmonary edema) and systemic poisoning (from CO and cyanide)[1, 3] which is the main and most lethal problem with smoke inhalation, however these do not primarily cause pulmonary symptoms.[4]

Depending on duration of exposure, particle size and water solubility symptoms can arise rapidly or after a delay.[5] Highly soluble gases and particles >5 µm tend to cause acute upper airway manifestations whereas less soluble gases e.g. phosgene, HCL, and aldehydes[6, 7] and particles <3 µm[8, 9] mainly manifests as lower airway injury either acutely or delayed.[1, 3] In this review we will focus on delayed onset pulmonary edema. Many authors claim that the delay from smoke exposure to clinical presentation of pulmonary edema can be up to 48-72 hours[1, 3, 10] thereby giving rise to the problematic scenario of sending home or not admitting a seemingly healthy and unaffected patient who is at risk of developing delayed onset pulmonary edema and, in worst case, death. Many authors recommend observation for 6-24 hours depending on the type and extent of inhalation injury,[3-5, 11] however fail to supply any evidence on which to base their claims. A retrospective case note review by Mushtaq et al. propose that patients with short exposure to fumes, Glasgow Coma Scale (GCS) 15, and both clinical examination and vital parameters are normal, be discharged without further investigations such as arterial blood gas or pulse oximetry.[12] The aim of this review is to collate the existing literature on delayed onset pulmonary edema due to toxic smoke inhalation, the incidence and possible duration of delay.

Objectives

The primary objective was to assess the risk of delayed onset pulmonary edema after toxic smoke inhalation while the secondary objective was to assess the duration from exposure to toxic smoke, without significant skin burns, to development of symptoms of delayed onset pulmonary edema. The tertiary objective was to determine which patients that could be discharged safely with minimal risk of developing delayed onset pulmonary edema after discharge.

Methods and eligibility criteria

A protocol was established (available by request to the primary author) which describes the method, inclusion and exclusion criteria, selection process,

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and data extraction all according to PRISMA guidelines.[13] A literature search based on PEO (Population, exposure, and outcome) was done.

P: All population groups are of interest regardless of demography, education, nationality, comorbidities, population size, or setting.

E: Potential inhalation of toxic smoke defined as an aerosol of solids, gases, and droplets emitted when a substance undergoes combustion or pyrolysis.

O: Delayed PE should be diagnosed through clinician's objective examination, vital parameters, arterial puncture, radiography, spirometer, extravascular lung water (EVLW) or by other objective methods at a hospital or by a clinician. Pulmonary edema emerging within 4 hours-7 days after exposure to toxic smoke was regarded as delayed onset pulmonary edema. Pulmonary edema emerging within 4 hours of exposure was not regarded as delayed onset pulmonary edema.

All studies describing smoke exposure and delayed onset pulmonary edema were included. Animal studies and studies in languages other than English were excluded. Prospective cohorts, case-reports, case-series and cross-sectional studies were of most interest. Inclusion and exclusion criteria are listed in Appendix 2.

Information sources and search strategy

A search strategy was designed which was approved by an experienced information scientist. The strategy included MeSH, Emtree, and free text terms combining terms related to smoke, lung, and edema in a sensitive manner as possible. The database search was conducted in Medline, Embase, and Cochrane Central Register of Controlled Trials covering all dates from day of inception of the respective databases to date of search 14 April 2016 (appendix 1).

Study selection

All studies resulting from the search strategy applied in the three different databases were exported to and collated in EndNote X7.5 (Thomson Reuters, Toronto, Canada). Duplicates were not removed in EndNote. All studies were exported from EndNote to Covidence (https://www.covidence.org) in which screening and removal of duplicates was performed. We reviewed all titles according to eligibility criteria and excluded animal studies and studies not regarding smoke inhalation or pulmonary edema. Thereafter we read the resulting abstracts, assessed their eligibility for review in full text and excluded studies in languages other than English. All studies reviewed in full text were searched for potentially relevant studies in the reference lists (snowballing). The process of study selection and data collection was performed by one reviewer only.

Data collection process and Data items

The following data were extracted manually from each study: Primary author, timing, study design, setting, total number of participants, proportion of men, age, type of exposure (composition and closed space), duration of exposure, extent of burned body surface area (BSA), symptoms, findings, treatment or intervention, outcomes, incidence of delayed onset pulmonary edema, time to event, autopsy findings, methodological quality, risk of bias, and conclusion (Table 1).

Results

The search strategy yielded 11,235 items. In the selection process, these were reduced to 54 articles, which were read in full. Five articles from the literature search and additional two articles[4, 14] retrieved from references in Ruddy et al.[15] and Lee et al.[16], respectively, were included in this review. Forty-nine articles were excluded due to wrong study design, outcome, exposure or patient population (Appendix 2).

Study characteristics

All seven studies were indexed in both Embase and Medline but none were indexed in Cochrane library. All were published in English between the years 1955-1988 and were case-reports, case-series or cohort studies.

The study populations varied between 1 and 51 with a total of 135 and were aged 6 hours-76 years. All were exposed to smoke inhalation injury with or without surface burns.

Results of individual studies

Cox et al. *[Br Med J. 1955 Apr 16; 1(4919): 942–946]* describe 15 neonates exposed to smoke from a smoldering wooden floor covered in linoleum, the majority without cutaneous burns. Five babies developed respiratory distress within 24 hours and additional five after being relatively unaffected or even showing improvement during the initial 24 hours. Three children are described as being in good/fairly good condition without burns or respiratory symptoms during the first 24 hours postinjury only to develop deteriorating respiratory function shortly after 24 hours and additionally three were asymptomatic with symptoms appearing within 24 hours. Thirteen babies died, one died in the fire and twelve died after 18.5 to 57 hours postinjury. Autopsy confirms the cause of death being PE, occlusive casts, pleural hemorrhage, and pulmonary infection. Pulmonary edema was most prominent in three cases.

A case report by Dyer et al. *[JAMA. 1976;235(4):393-7]* describe a fireman exposed to

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Table 1. Characteristics of included studies.

Author, year, study design (reference)	Setting, (country) timing	Study population (M/F) age	Type of exposure (duration in minutes) %BSA burnt	Other symptoms / findings	Radiology/ endoscopy	Treatments acquired	Pulmonary edema (delay in hours)	Complications /Mortality
Cox, M.E. et al. 1955, cohort (14)	Dellwood, general-practitioner obstetric unit, (England) 1954	15 (8/7) 6 hours-9 days	Smoke from smoldering wooden and linoleum floor (20-30min) 1 extensive burns/charring 2 superficial burns on face and chest	Immediate or delayed coughing, dyspnea, cyanosis with increasing distress after 24h	1 CXR 6d: atelectasis with clearing on CXR day 11	O_2, antibiotics, cortisone, suction of mucous. glucose-saline and milk mixture through esophageal tube	**2** (0h) **5** (0-24h) **5** (>24h)	13 dead (1 with extensive burns dead on arrival, 12 bronchial occlusion, PE and infection)
Dyer, R et al. 1976, Case report (7)	Washington DC. (USA) 1970	1(1/0) Firefighter w/o mask. 33 years old.	Smoke from plastic/teflon copy machine, PVC (20min) 0%BSA	Conjunctivitis, lacrimation, headache and dyspnea for 24 hours. Fainted after 24 hours.	None	None	**1** (24h)	1 dead >24h
Lee, M. J. et al. 1988, cohort (16)	Mater Misericordiae Hospital, Dublin (Ireland) 1981	45 (32/13) 15-25 years old	SO2, N2O and hydrocyanic acids from combustion of polystyrene roof tiles, plastics and seating foam(?) 38 <25%BSA 6 25-50%BSA 1 95%BSA	Facial burns, carbonaceous sputum, hypoxia and hypercarbia in arterial blood gas	45 CXR <1h: abnormal in 33 (29 bronchial wall thickening, 13 subglottic edema, 2 pneumoTHX, 2 PE, 3 patchy consolidations)11 CXR normal	intubation	**5** ("slightly delayed" 1-24h) **2** (0h)	2 dead (95%BSA burn/PE) 18 respiratory infections 2 pneumothoraces 1 pneumomedia-stinum
Tranbaugh, R.F. et al. 1983, cohort (17)	San Francisco general hospital burn unit, California, (USA) 1977-1981	14 (6/8) avg 49 years old	Thermal injury with severe inhalation injury (?) 14 Avg 37% (8-52%)BSA	12 mean carboxyhemoglobin 30%	1 elevated EVLW on admission 5 elevated EVLW 3-21d CXR not described	Excessive fluid administration leading to PE on day 2	**1**(0h) **5** after 2-24 days (increased EVLW due to 2 pneumonias, 2 burn wound sepsis and 1 cardiogenic PE)	10 pneumonias 9 dead (6 sepsis, 1 acute renal failure, 1 hepatorenal syndrome, 1 anoxic brain damage

smoke from a burning copy machine, partially made of PVC, immediately developed cough, dyspnea, headache, dizziness, vertigo, nausea, and a burning sensation in the throat but showing improvement during the first day. Approximately 24 hours after exposure he suffered monosymptomatic syncope saying he "felt fine" afterwards only to be found dead a few hours later. Autopsy determines pulmonary hemorrhage and pulmonary edema to be the cause of death.

After a discotheque fire in Ireland Lee et al. *[Clinical Radiology. 1988;39(1):33-7]* describe 45 patients admitted to a hospital with smoke inhalation and cutaneous burns to varying extent, 2 with pulmonary edema on admission. The smoke resulted from combustion of polystyrene and plastics and contained sulphur dioxide, nitrous oxide and hydrocyanic acids. Five patients showed bronchial wall thickening on chest x-ray on admission and developed pulmonary edema after admission but within 24 hours of admission. One patient with pulmonary edema alone and one with pulmonary edema and burns covering >95% BSA died. Eleven patients with normal chest x-ray had <15% BSA burns and are described as all having respiratory symptoms on admission.

Tranbaugh et al. *[Journal of Trauma-Injury Infection & Critical Care. 1983;23(7):597-604]* present a cohort study with 14 adults with average 37% burnt BSA and smoke inhalation with an average of 30% COHb. All suffered facial burns, closed space burns, carbonaceous sputum, and 12/14 had on average COHb 30% on admission. One patient presented with pulmonary edema on admission, 10 patients developed pneumonia, and 5 patients developed PE within 2-24 days postinjury presumably from burn wound or pulmonary sepsis. Nine patients, including above mentioned 5 patients with pulmonary edema, died from sepsis, acute renal failure, hepatorenal syndrome or anoxic brain damage.

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Author, year, study design (reference)	Setting, (country) timing	Study population (M/F) age	Type of exposure (duration in minutes) %BSA burnt	Other symptoms / findings	Radiology/ endoscopy	Treatments acquired	Pulmonary edema (delay in hours)	Complications /Mortality
Webster, J. R. Et al. 1967, Case series (10)	Northwestern University Medical School and Chicago Wesley Memorial Hospital (USA) 1965-1967	3 (3/0) 34-52 years old	One industrial fire and two hotel room fires with burning mattress. All presenting oro-pharyngeal mucosal redness and damage No mention of surface burns	2-24 hours postinjury: dyspnea, chest tightness, restlessness, cyanosis, wheezes and ronchi	CXR 0h: normal CXR 36h: extensive bilateral basal infiltrates	CPAP, oxygen, nebulized saline and isoproterenol, i.v. fluids, antibiotics, tracheal suction steroids, digitalis, aminophylline, tracheostomy with mechanical ventilation	**1** (2h) **1** (36h)	-
Vivori, E. Et al. 1977, case series (18)	Alder Hey Children's Hospital, Liverpool (England) 1973-1977	6 (5/1) 1-11 years old	Indoors smoke from burning furniture and thermal injury (?) 4 10- 60% BSA	1 semi-conscious, obstructed breathing, COHb 6-7% 1 cyanosed, restless, thick soot-stained sputum 2 unconscious	1 laryngoscopy: pharyngeal and laryngeal edema	Intubation, mechanical ventilation, humidified oxygen, antibiotics, dexamethasone, mannitol	**2** (24h) immediately after extubation **1** (60h) 12h after extubation	4 respiratory and/ or cardiac arrest with one death due to respiratory arrest 2 hypoxic brain damage 1 decerebrate rigidity with complete recovery
Zikria, B. A. Et al. 1972, cohort (4)	Columbia-Presbyterian Medical Center.New York, (USA) 1960-1972	51 (37/14) 6-76 years old	40 Smoke inhalation 6 CO poisoning 5 Respiratory burn 45 thermal injury (?) 6 0%BSA 45 1-30%BSA	17 COHb >15% 10 burns to face, upper trunk and extremities	CXR 0h: 3 PE CXR >0h: 8 PE/ pneumonitis	Antibiotics, bronchodilator, digitalis, diuretics, corticosteroids and intubation	**11** PE/ pneumonitis on CXR. 3 on admission and 8 >0h "later"	5 deaths (3 cardiorespiratory arrest, 1 PE, 1 pneumonia) 6 respirator: (3 tracheostomies and 3 intubations)

Webster et al. *[JAMA. 1967;201(5):287-90]* cared for 16 patients with smoke inhalation injuries. Two were dead on arrival and an additional patient died after admission. Ten were occupational injuries in industrial workers or firemen. In their article they describe three cases.

Case 1: A 34 year old fireman fainted whilst fighting an industrial fire with acrid smoke. He was seemingly unaffected without signs or symptoms of pulmonary insult until 2 hours postinjury when he presented with chest tightness, dyspnea, and temperature 37.6°C. Chest x-ray reveals signs of pulmonary edema which cleared on the fourth day. He was treated successfully with antibiotics, tracheal aspirations, and intermittent positive pressure breathing.

Case 2: A 52 year old executive found by police in a burning hotel room. On admission he was stuporous, slightly cyanotic, tachypnoeic, afebrile, and hemodynamically stable. Pulmonary auscultation reveals coarse sounds with wheezing. Nasal oxygen, intravenous fluids, antibiotics, intermittent positive pressure breathing, and nebulized sodium chloride were initiated. During the initial 24 hours he was stable but 12 hours thereafter he developed increasing cyanosis, dyspnea, fever 38.9°C, and respiratory rate 45/min with moist rales. Chest x-ray showed bibasilar infiltrates and he received a tracheostomy and was put on respiratory assistance with improvement.

Case 3: A 49 year old male bed smoker who mistakenly fell asleep and lit the mattress on fire with the cigarette. On admission he was disoriented, mildly cyanotic, moderately distressed with a breathing rate of 30/min, tachycardia, and temperature 38.3C. Despite adequate treatment his condition deteriorated to the point where he received tracheostomy and mechanical ventilation with 50%-30% oxygen with improvement after 3 weeks.

Vivori et al. *[British Medical Journal. 1977;2(6100):1462-4]* describe 6 cases of children retrieved from house fires with burning furniture. All had either burns covering >25% BSA, severe respiratory symptoms or altered consciousness except one patient with only 10% BSA burned and

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Table 2. Risk of bias.

Studies Type of bias	Cox, M.E. et al. 1955[14]	Dyer, R et al. 1976[7]	Lee, M. J. et al. 1988[16]	Tranbaugh, R.F. et al. 1983[17]	Webster, J. R. et al. 1967[10]	Vivori, E. et al. 1977[18]	Zikria, B. A. et al. 1972[4]
Skin burns	Yes	NR	Yes	Yes	NR	Yes	Yes
I.v. fluids	NR	NR	NR	Yes	Yes	NR	NR
Infection	Yes	NR	Yes	Yes	NR	NR	Yes
Pediatric population	Yes	No	Partially	No	No	Yes	Partially
Intubation-extubation	No	No	Yes	No	No	Yes	Yes
Smoke source described	Yes	Yes	Yes	No	Yes	Yes	No

seemingly unaffected respiration but developed laryngeal edema and stridor 3 hours later. Five patients were intubated and mechanically ventilated for at least 24 hours. After being intubated and mechanically ventilated for 24 hours 2 children developed pulmonary edema shortly after extubation and were subsequently intubated and ventilated for an additional 24 hours with successful extubation. One patient was intubated and ventilated for 48 hours and developed pulmonary edema 12 hours after extubation. He died 2 days later.

Zikria et al. *[Ann Surg. 1975 Feb;181(2):151-6]* describe 51 patients admitted with mostly smoke inhalation and a few patients with concomitant burns. Three patients had radiographically confirmed pulmonary edema on admission. Additionally 8 patients developed radiographic evidence of either PE or pneumonitis during the hospitalization. Forty patients were described as mainly suffering from smoke inhalation injury and 17/21 had COHb >15% however it is not described if anyone was asymptomatic before developing pulmonary edema. Eight tracheostomies and 3 intubations were performed and 7 were treated with intermittent positive pressure breathing. Despite adequate treatment 5 patients died out of which one died of pulmonary edema.

Risk of Bias in individual studies

Most studies included are biased in at least one aspect and it is difficult to grade the quality or risk of bias in a uniform manner due to them being case report/series or cohort studies. There are many potential factors that can affect the results of the individual studies and the outcomes of this review which have to be kept in mind when interpreting the results (Table 2).

Many studies present patients with cutaneous or inhalation burns which, besides being risk factors for pulmonary edema, also is an indication for aggressive intravenous fluid resuscitation, possible infection or intubation-extubation which are potential causes of pulmonary edema. Two studies describe pediatric patients with smaller airways and different response, with smaller margins to airway assault in comparison to adults. Combustion of different materials produces gasses with different properties and symptomatologies. Some studies describe the source of the smoke and the potential constituents while other studies fail to do so.

The time of occurrence of pulmonary edema is, in some studies, described in intervals so the exact time-to-event can vary significantly.[4, 14, 16] Cox et al. did not specify if the five pulmonary edema developing during the first day developed before or after our arbitrary cutoff of four hours postinjury leaving the possibilities of 0-5 cases of pulmonary edema occurring after four hours.[14] Lee et al. stated that pulmonary edema in five patients was delayed but appeared within 24 hours which we interpret as 1-5 cases of pulmonary edema might have developed after four hours.[16] Five patients described by Tranbaugh et al. develop pulmonary edema after 2-24 days presumably due to infection which we interpret as 1-4 patients developing pulmonary edema within seven days from exposure.[17] Zikria et al. describe eight delayed chest x-rayfindings as being either pulmonary edema or pneumonitis so the exact occurrence of pulmonary edema can vary between 1-7 cases.[4]

In Cox et al., the autopsy reports claim pulmonary edema and airway casts with occlusion to be the cause of death and it can be argued whether the cause of death is pulmonary edema, airway occlusion due to formation of casts, or more likely, both. However it can safely be presumed that pulmonary edema or cast formation did not occur too long before symptoms appeared, ergo time to symptoms is approximately equal to the time to pulmonary edema or cast formation.[14]

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Risk of bias across studies

Publication bias is a potential issue because authors would be more likely to publish studies concerning patients with smoke inhalation who subsequently develop pulmonary edema after admission rather than studies describing patients with the same exposure but with immediate pulmonary edema or perhaps no complications and a mild and uneventful recovery. This would provide us with a falsely elevated incidence of delayed onset pulmonary edema leading to more patients admitted for observation ergo better patient safety but more expensive care. As only studies reporting pulmonary edema after exposure to toxic smoke were included, this will increase the estimates for incidence.

Discussion

A total of 39 out of 135 patients from all studies involved or 29% of the patients involved in this review developed pulmonary edema after admission. It has to be kept in mind that delayed onset pulmonary edema was an inclusion criterion hence incidence rates calculated using this data will be grossly overestimated due to selection bias. Applying data only from cohort studies of adult patients[4, 16, 17] in the calculations will render a more accurate estimation of 3-16/110 or 2.7-14.5% however this is most likely also an overestimation.

Only seven patients with smoke inhalation (5.2%) were completely asymptomatic and without burn wounds before developing pulmonary edema. Cox et al. describe three neonates who were asymptomatic for 24 hours and three for less than 24 hours before developing respiratory symptoms and pulmonary edema. A firefighter cared for by Webster et al. was, besides an episode of syncope, unaffected for two hours before developing dyspnea and chest tightness at rest later radiographically confirmed as pulmonary edema. Neonates and children would most likely be admitted if there was any suspicion of smoke inhalation but adults would perhaps not. Applying data only from adults gives us one patient or 0.9% of adults being asymptomatic until developing pulmonary edema which is more realistic. The firefighter would most likely be admitted for observation due to the syncope and would therefore not pose an issue i.e. discharging a potentially deteriorating patient.

Most patients developed symptoms within 24 hours but one was stable until 36 hours postinjury only to deteriorate massively. Pulmonary edema after 36 hours is most likely to be caused by other mechanisms related to burn injury such as excessive intravenous fluids, de novo heart failure,[16, 17] infection or problems related to intubation.[18] However pulmonary edema due to infection or sepsis is rarely seen in the first few days[17] and pulmonary edema from excessive fluids can be avoided using fluid requirement formulas such as Parkland and Holliday-Segar.[19] Care should be taken when a previously intubated patient is extubated due to the risk of pulmonary edema within 24 hours from extubation.[18]

None of the 39 patients developing pulmonary edema after admission were described as suffering only short exposure to fumes and presenting GCS 15, normal clinical examination, and vital parameters ergo the triage model suggested by Mushtaq et al. would have identified all these patients.[12]

The fireman exposed to PVC smoke described by Dyer et al. was the patient with the least amount of bias involved however the circumstances under which he died were poorly described. Chlorides are known lung irritants and are the most likely cause of pulmonary edema in this case.

Besides the delayed chemically induced pulmonary edema caused by the different constituents of fire smoke there are many other conditions associated with cutaneous and inhalation burns which can easily be confused clinically with this such as overzealous intravenous crystalloid resuscitation, de novo heart failure, pneumonia, sepsis, and burn injury alone.[20-22] Pruitt et al. describe pulmonary edema in 48 patients out of 697 burn victims 4-6 days after burn injury despite only four patients suffering inhalation injuries further complicating identifying exactly what triggered the pulmonary edema.[21]

All studies are of older date and different materials were used when building houses which could affect the incidence rate of delayed onset pulmonary edema. Medical knowledge and technology, such as pulse oximetry or determination of carbon monoxide levels, have also come a long way in recent decades and diagnostic methods might have had worse sensitivity and specificity than we have today opening up to potential misdiagnosis in these studies. Pulse oximetry or CO-oximetry are quick and inexpensive means of diagnosing severe smoke inhalation but were not commercialized before early 1980s and was not available for most of these 135 patients. It can be presumed that most patients visiting emergency departments nowadays would be subjected to these tests and if abnormal the patients would possibly admitted for observation.

It is evident that chest x-ray on admission is a poor diagnostic tool to diagnose inhalation injury due to its low sensitivity[2, 23] ergo a normal chest x-ray does not exclude inhalation injury. However subglottic edema or bronchial wall thickening present in chest x-ray on admission indicates damage to upper and lower airways respectively and one should strongly consider close observation and admission due to the

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risk of upper airway swelling and/or parenchymal lung injury.[16] In Lee et al. 33 out of 45 patients had bronchial wall thickening on admission chest x-ray and five out of these 33 developed pulmonary edema after admission.[16]

A patient with smoke inhalation and skin burns with seemingly unaffected respiration will most likely be admitted for treatment of the burn wounds and therefore already be hospitalized when or if delayed onset pulmonary edema presents and the unfortunate situation of discharging a seemingly healthy patient would not be an issue.

Strengths and limitation

The search strategy was designed with the help of an experienced information scientist in a sensitive fashion as possible in order to gather as many relevant studies as possible concerning this fairly rare phenomenon and it is clearly described in detail in appendix 1 in a reproducible manner.

The selection process was done by one reviewer only and even though we tried not to exclude potentially relevant articles during the process it is not impossible that we might have missed some. In order to achieve a more accurate incidence rate of delayed onset pulmonary edema one would need to include all studies regarding smoke inhalation with and without pulmonary edema or delayed onset pulmonary edema to be used in the calculations. This would provide an estimate closer to the real world incidence which would be more applicable in the emergency departments.

Conclusion

Based on data from the cohort studies and with the potential variability of the numbers taken into account it can be concluded that delayed onset pulmonary edema develop in 2.7-14.5% of these patients with toxic smoke inhalation injuries. However, due to a high risk of publication bias, this number is probably very exaggerated.

None of the included patients were completely asymptomatic and without skin burns before developing symptoms of pulmonary edema. It has to be kept in mind that these data are prone to confounding factors such as concomitant surface burns and selection bias because studies were included only if they presented delayed onset pulmonary edema hence these rates are most likely overestimated.

Funding

No funding was received by anyone involved in writing this review.

Conflict of interest

None declared.

Appendix 1. Search strategy.

Database	Date of search	Search strategy
MEDLINE Ovid	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present (14.3.2016)	1. (pulmon* or lung* or alveol* or respirat* or trache*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. (wet* or distress* or edema* or oedema* or swell* or hydrops* or drops* or turgid* or water retention or ARDS or respiratory distress syndrome).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 3. (smok* or fire* or burn* or soot* or fume* or smolder* or combust*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 4. exp Lung/ 5. exp Pulmonary Edema/ or exp Edema/ 6. exp Respiratory Distress Syndrome, Adult/ 7. exp Smoke/ 8. exp Soot/ 9. exp Fires/ 10. exp Inhalation Exposure/ or exp Smoke Inhalation Injury/ or exp Inhalation/ or exp Burns, Inhalation/ or exp Inhalation Exposure/ 11. 1 or 4 12. 2 or 5 or 6 13. 3 or 7 or 8 or 9 or 10 14. 11 and 12 and 13 **2815 articles**

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EMBASE Ovid	Embase Classic + Embase 1947 to 2016 March 11	1. (pulmon* or lung* or alveol* or respirat* or trache*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 2. (wet* or distress* or edema* or oedema* or swell* or hydrops* or drops* or turgid* or water retention or ARDS or respiratory distress syndrome).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 3. (smok* or fire* or burn* or soot* or fume* or smolder* or combust*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 4. exp lung parenchyma/ or exp lung/ or exp lung lobe/ 5. exp edema/ or exp lung edema/ 6. exp swelling/ 7. exp respiratory distress syndrome/ or exp adult respiratory distress syndrome/ 8. exp soot/ or exp smoke/ 9. exp fire/ 10. exp fume/ 11. exp combustion/ 12. exp inhalation/ or exp toxic inhalation/ 13. 1 or 4 14. 2 or 5 or 6 or 7 15. 3 or 8 or 9 or 10 or 11 or 12 16. 13 and 14 and 15 **8257 articles**
Cochrane library	Cochrane Central Register of Controlled Trials : Issue 1 of 12, January 2016	#1. pulmon* or lung* or alveol* or respirat* or trache* (Word variations have been searched) #2. wet* or distress* or edema* or oedema* or swell* or hydrops* or drops* or turgid* or water retention or ARDS or respiratory distress syndrome (Word variations have been searched) #3. smok* or fire* or burn* or soot* or fume* or smolder* or combust* (Word variations have been searched) #4. MeSH descriptor: [Lung] explode all trees #5. MeSH descriptor: [Edema] explode all trees #6. MeSH descriptor: [Pulmonary Edema] explode all trees #7. MeSH descriptor: [Respiratory Distress Syndrome, Adult] explode all trees #8. MeSH descriptor: [Smoke] explode all trees #9. MeSH descriptor: [Soot] explode all trees #10. MeSH descriptor: [Fires] explode all trees #11. MeSH descriptor: [Inhalation] explode all trees #12. MeSH descriptor: [Burns, Inhalation] explode all trees #13. MeSH descriptor: [Smoke Inhalation Injury] explode all trees #14. MeSH descriptor: [Inhalation Exposure] explode all trees #15. #1 or #4 #16. #2 or #5 or #6 or #7 #17. #3 or #8 or #9 or #10 or #11 or #12 or #13 or #14 #18. #15 and #16 and #17 **163 articles (trials)**

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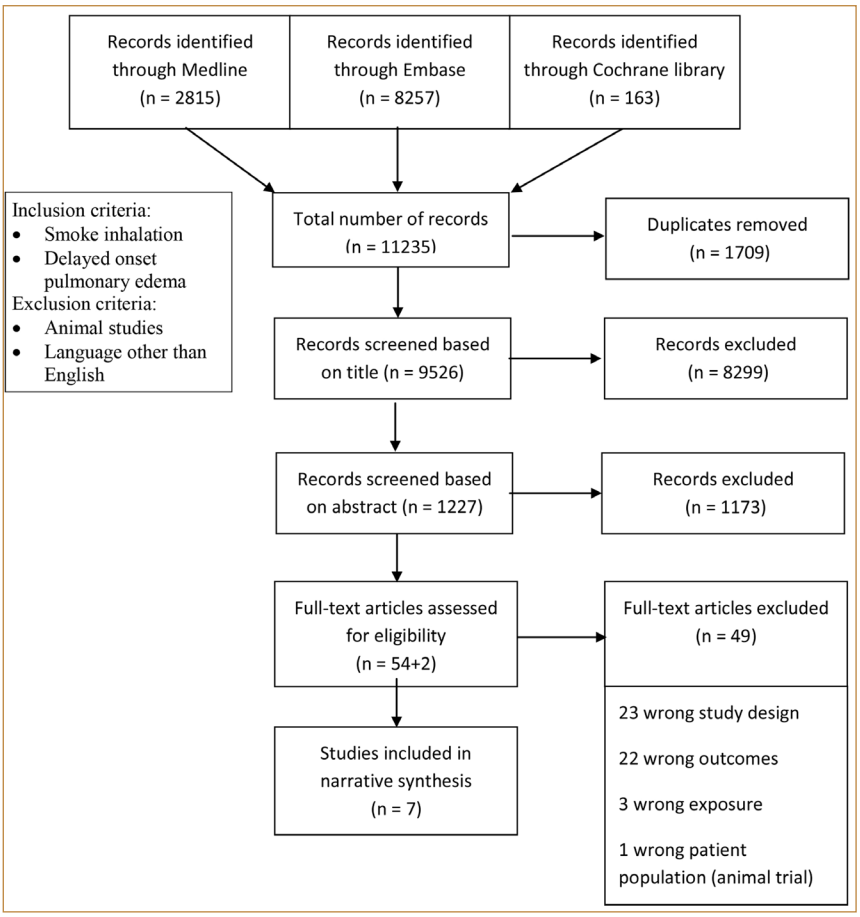

Appendix 2. Flow diagram and criteria for inclusion and exclusion.

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