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Phosgene Toxicity Clinical Manifestations and Treatment: A Systematic Review

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Abstract

Exposure to phosgene, a colourless poisonous gas, can lead to various health issues including eye irritation, a dry and burning throat, vomiting, coughing, the production of foamy sputum, difficulty in breathing, and chest pain. This systematic review aims to provide a comprehensive overview of the clinical manifestations and treatment of phosgene toxicity by systematically analyzing available literature. The search was carried out on various scientific online databases to include related studies based on inclusion and exclusion criteria with the use of PRISMA guidelines. The quality of the studies was assessed using the Mixed Methods Appraisal Tool (MMAT). Thirteen articles were included in this study after the screening process. Inhalation was found to be the primary health problem of phosgene exposure with respiratory symptoms such as coughing and dyspnea. Chest pain and pulmonary oedema were also observed in some cases. Furthermore, pulmonary crackle was the most common reported physical examination. Beyond respiratory tract health issues, other organs involvements such as cardiac, skin, eye, and renal were also reported in some studies. The symptoms can occur within minutes to hours after exposure, and the severity of symptoms depends on the amount of inhaled phosgene. The findings showed that bronchodilators can alleviate symptoms of bronchoconstriction caused by phosgene. Oxygen therapy is essential for restoring oxygen levels and improving respiratory function in cases of hypoxemia. In severe cases, endotracheal intubation and invasive mechanical ventilation are used for artificial respiration, along with the removal of tracheal secretions and pulmonary oedema fluid through suctioning as crucial components of supportive therapy.

Keywords: Chemical Agent, Clinical Manifestations, Exposure, Phosgene, Therapy

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Introduction

Phosgene is a highly toxic gas that has been used as a chemical weapon in the past and is still used in the production of various chemicals (1). The manufacture of phosgene is roughly 1 million tons per year in the USA, and more than 10,000 workers are involved in its production and use application (2). The clinical manifestations of phosgene toxicity can range from mild respiratory symptoms to severe lung injury and death (1). Early clinical manifestations of phosgene exposure include cough, dyspnea, and eye irritation, while more severe cases can result in lung oedema, bronchoconstriction, and respiratory failure (3). The severity of phosgene toxicity is dependent on several factors, including the dose, duration, and route of exposure, as well as the individual's age, health status, and preexisting medical conditions (2).

The treatment of phosgene toxicity is primarily supportive, to relieve symptoms and prevent further lung damage (4-6). This may involve providing supplemental oxygen, and mechanical ventilation, as well as addressing any underlying medical conditions (5). In severe cases, treatment may also involve corticosteroids, diuretics, and other medications to reduce lung oedema and improve respiratory function (3). According to the review of the studies, there is a lack of a comprehensive and up-to-date study on the clinical symptoms of phosgene toxicity and its treatment, so there is a need to present a review study for better comprehension of the reported toxicity, and clinical manifestation, and treatment/management of phosgene exposure.

This systematic review compiles the existing literature on phosgene toxicity, offering a thorough examination of clinical manifestations and treatment modalities for phosgene exposure. It serves as a valuable resource for healthcare providers, aiding them in selecting appropriate care and thereby enhancing the likelihood of successful treatment.

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Materials and Methods

Search strategy

The search was carried out to identify relevant studies on the clinical manifestations and treatment of phosgene toxicity. In this manuscript, we reviewed the original, case studies, guidelines, and observational cohort studies. In addition to reviewing medical and health literature, we reviewed articles and reports from other scientific disciplines like chemistry and chemical engineering. Various databases were employed to explore and locate pertinent scientific articles and reports. These databases included Scopus, MEDLINE, PubMed, Science Direct, AIM, ProQuest, ELDIS, and CINAHIL. The funded articles were preserved and examined to ascertain the existing understanding of toxicity, clinical manifestation, and treatment/management of the health problems resulting from phosgene exposure. Moreover, we examined the reference lists of retrieved articles and relevant systematic reviews to pinpoint additional pertinent studies. We conducted searches using various keywords, either alone or in combination, in the specified databases to find the articles. These keywords included "Phosgene", "signs and symptoms", "signs", "clinical manifestations", "manifestations", "symptoms", "toxicity", "in toxicity", "adverse effects", "poisoning", "toxication", "therapeutics", "therapy", "treatment", "drug therapy", "pharmacotherapy", and "management".

Inclusion criteria

The following criteria were used to determine the eligibility of studies for inclusion in this systematic review: reports on the clinical manifestations or treatment of phosgene toxicity [observational studies, case reports, and case series (7)], published on human studies in English language. After screening, published manuscripts with available full texts (up until December 2023) were considered for analysis.

Exclusion criteria

The reviews, opinion or editorial articles, letters, non-English and animal studies were excluded from this systematic review.

Data extraction and selection

The following steps were taken to extract and collect data from the founded studies:

All identified studies were screened and duplicate studies were removed. The titles and abstracts were reviewed for eligibility and full-texts were obtained. Data from the included studies including the author(s) information, publication year, title, journal, source origin, study design, study population/sample size, compatibility with inclusion and exclusion criteria, and outcomes (clinical manifestations/treatment) were extracted and recorded. All of the included studies were reviewed by a second reviewer to ensure the reliability of the extracted data.

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and rigour in the review process. The Mixed Methods Appraisal Tool (MMAT) was used to ensure the methodological quality of the included studies. Figure 1 shows the search and selection procedures as a flowchart. Finally, 13 studies were included for the review analysis and presentation.

Results

The results of this systematic review of 13 studies showed that it is important to understand the phosgene exposure status, including inhalation and dermal contact. Therefore, proper safety measurements and providing comprehensive worker training can effectively reduce the risk of phosgene exposure and related health hazards (8, 9).

Mechanism

Pulmonary oedema is a critical aspect of phosgene-induced acute lung injury (P-ALI), with diverse causative factors. Phosgene swiftly interacts with alveolar surfactant upon inhalation, depleting it and subsequently reacting with lipids, proteins, and nucleic acids in alveolar tissue. This process impairs the plasma membrane, leading to the destruction of the pulmonary blood-gas barrier and the development of pulmonary edema (10, 11). Simultaneously, the interaction releases numerous inflammatory mediators and reactive oxygen species (ROS), intensifying alveolar capillary permeability and exacerbating pulmonary oedema (11). The subsequent sections delve into the molecular mechanisms of inflammatory mediators and oxygen-free radical release. Besides oedema resulting from a compromised air-blood barrier, neurogenic pulmonary oedema is a significant contributor to P-ALI. Its mechanisms, though speculative, may involve the excitation of vagal C-fibers responsible for lower respiratory tract innervation (12). Exposure to high phosgene concentrations sustains vagal C-fiber excitation, leading to symptoms like apnea and bradycardia. This heightened excitability reduces pulmonary sympathetic tone, causing the failure of vasodilatation mechanisms, systemic pulmonary vasoconstriction, and closure of lung cavities (11). The consequent blood retention in the pulmonary circulation elevates pulmonary venous pressure, resulting in the exudation of fluids and proteins and the development of neurogenic pulmonary oedema in P-ALI (13).

Sign and symptoms

The primary and secondary signs and symptoms, as well as the treatments for patients exposed to phosgene, were analyzed in this systematic review.

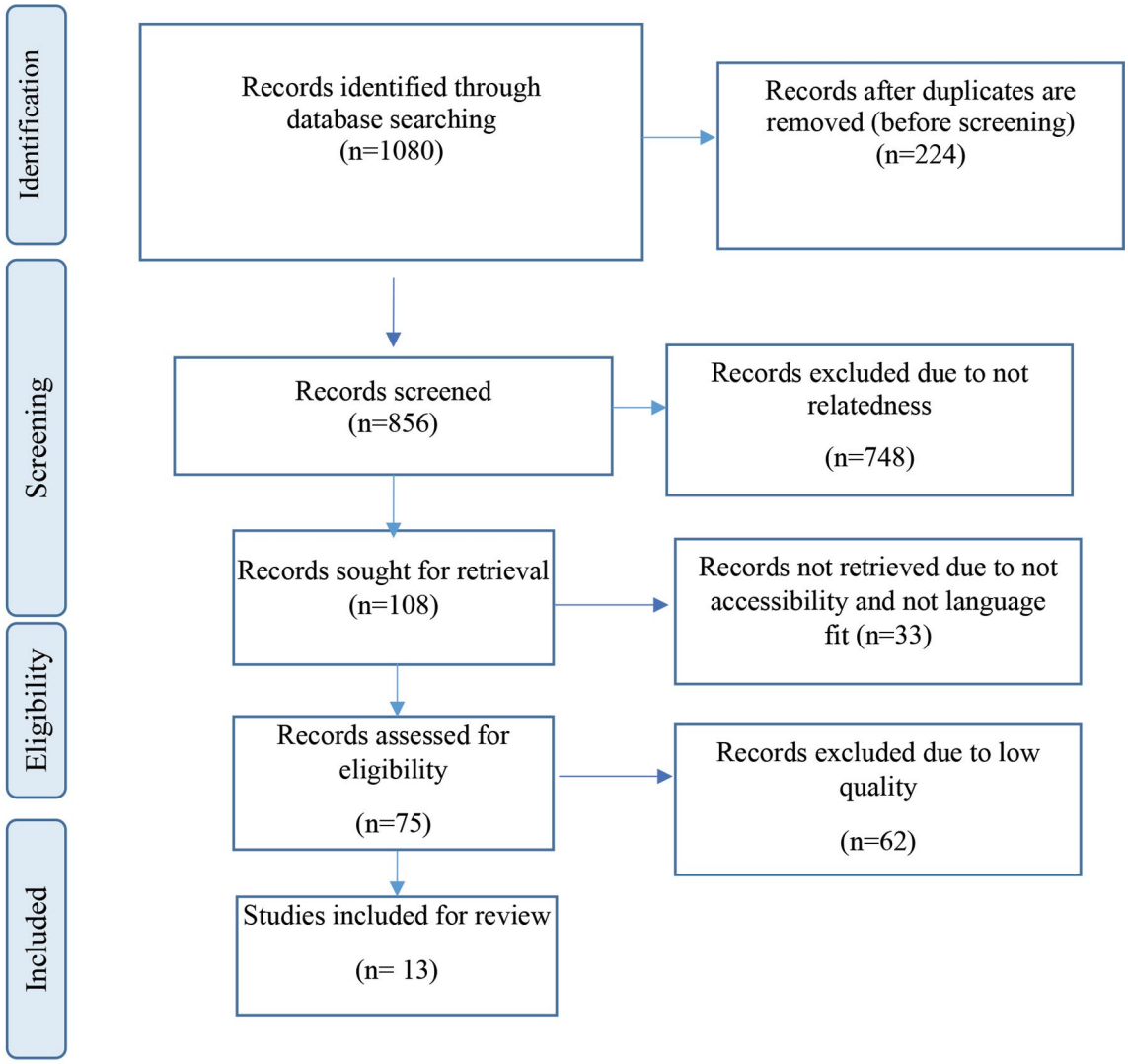

Fig.1: Flow charts for the studies were identified, displayed, and included in the present study.

Initial signs and symptoms

Initial signs and symptoms of phosgene exposure can range from mild to severe. The onset of symptoms can occur within minutes to hours after exposure, and the severity of symptoms depends on the amount of phosgene inhaled. The following signs and symptoms were identified across multiple studies.

Phosgene exposure leads to a range of clinical manifestations that can be classified into respiratory, cardiac, skin, eye, digestive, and other categories. The results suggest that respiratory manifestations such as coughing, shortness of breath, and pulmonary crackle are commonly reported in phosgene exposure (14-20). Chest pain and pulmonary oedema were also observed in some cases (20). The results suggest that the symptoms of phosgene exposure vary across individuals, but respiratory involvement and changes in hemodynamic status are commonly reported (Table 1).

The initial clinical manifestations can be divided into three categories as follows:

Mild signs and symptoms: Patients exposed to phosgene may experience minor throat irritation and an anxious appearance (17, 21). They may also show decreased oxygen saturation (15, 21), but normal pulse and respiration rates (21).

Moderate signs and symptoms: In moderate cases of phosgene exposure, patients may experience choking sensations (14), cough (2, 4-7, 18-26), and ocular symptoms such as redness (14, 17, 18, 27). Dyspnea (14, 15, 18-20, 22-26), diffuse chest pain or chest tightness (14, 17, 19, 21, 23, 25, 26), vomiting (14, 20, 25), and tachypnea (15, 23, 26) are also common manifestations (3).

Severe signs and symptoms: Severe cases of phosgene exposure may cause nausea (15, 17, 18, 20, 25, 26), and a burning sensation in the mouth and throat (15, 18, 23, 24). Some patients may initially feel well but later return to the hospital in distress and shortness of breath with crackles bilaterally (19, 23, 24, 26).

Late signs and symptoms

Patients hospitalized after phosgene exposure may exhibit a spectrum of symptoms across different body systems and changes in laboratory tests. The effects of these symptoms can be long-lasting and range from mild to severe. Results showed that the most prevalent late signs and symptoms of patients exposed to phosgene were increased dyspnea, cough, audible wheezing, and decreased oxygen saturation with the development of diffuse pulmonary oedema. These signs and symptoms were reported in multiple studies and were observed in a substantial number of patients who were exposed to phosgene. Additionally, other manifestations such as oliguria, tachycardia, tachypnea, and cyanosis were also reported (Table 2).

The studies demonstrated acute cough in phosgene-exposure patients (14, 15, 21). The cough was initially described as dry, and in some cases, it may become productive, especially with pulmonary oedema and or superimposed infection. Furthermore, the studies indicate the presence of respiratory sounds, including audible wheezing and coarse crackles.

A recent study (28) considered 287 workers of phosgene production and captive units exposed to chronic low-dose phosgene. The mean duration of the job of participants was 18.9 ± 9.6 years. The effect of phosgene on the respiratory system was assessed by measuring peak expiratory flow rate (PEFR). It was reported that PEFR was remarkably reduced with increasing age and duration in the job, as well as those having direct exposure.

In some of the included studies, several laboratory findings were implied such as leukocytosis, lymphopenia, hyponatremia, hypokalemia, trace of albuminuria, crystals of calcium oxalate in the urine, and metabolic acidosis (21, 25).

Treatment

The following is a summary of the treatment options for phosgene exposure as reported in various studies. Table 3 outlines the different categories of treatments and the specific drugs and techniques used within each category.

Bronchodilators are used to relieve symptoms of bronchoconstriction caused by phosgene exposure, such as wheezing, coughing, and shortness of breath. They work by widening the airways, making it easier for patients to breathe (19, 21). However, it was reported that some bronchodilators such as nebulized salbutamol can cause some harm and may not improve survival (29).

Table 1: Initial manifestations in patients exposed to phosgene, classified by organs

Category	Signs and symptoms	References
Respiratory	Cough, choking sensation, tachypnea, crackles, Tightness in the chest, dyspnea, hemoptysis, decreased oxygen saturation (SpO_2)	(4, 18, 22-24, 27)
Cardiac	Chest pain at rest or after slight exertion	(21)
Skin	Cyanosis, flushed face (pink)	(18, 23, 25, 27)
Eye	Redness, lacrimation, eye burning	(14, 16, 21, 27)
Digestive	Vomiting, nausea	(14, 15, 21, 23)
Neurological	Headache, fatigue	(15, 23, 25)
Psychiatry	Anxiety, delirious	(15, 23)

Table 2: Late manifestations in patients exposed to phosgene, classified by organs

Category	Signs and symptoms/diseases	References
Respiratory	Decreased O_2 saturation, dyspnea, cough, audible wheezing, bilateral pulmonary oedema, pneumonitis, bronchitis, pleurisy, pneumothorax, ARDS, decreased PEFR	(14, 15, 18, 19, 27, 28)
Cardiac	Slight general cardiac enlargement, chest pain	(14, 25)
Skin	Cyanosis	(23, 25)
Eye	Conjunctivitis	(27)
Renal	Decreased urine production	(20)
Others	Fever, dry and furred tongue, palpable and firm spleen, decreased chest movement, dilated pupils	(16, 25)

Table 3: Treatment options for patients exposed to phosgene

Category	Treatment options	References
Oxygen therapy (hypoxemic cases)	High-flow oxygen therapy, continuous oxygen	(14, 18-20, 25)
Ventilation support	Noninvasive ventilation, endotracheal intubation and mechanical ventilation, suctioning of tracheal secretions and pulmonary oedema fluid	(14, 18, 21)
Other treatments (weak recommendation)	Lorazepam, N-acetylcysteine (nebulized), diuretics, valium for sedation, aminophylline, fluids (oral and intravenous)	(19, 21)

Oxygen therapy is an essential treatment for restoring oxygen levels and improving breathing in hypoxemic cases of phosgene exposure. It was also reported that high-flow oxygen therapy can improve the SpO_2 levels in (hypoxemic) patients (15, 22, 26). In a case report study, a 39-year-old male patient who encountered triphosgene gas at his workplace underwent treatment using a non-invasive ventilator and received 5 litres of oxygen. The SpO_2 of this patient improved from 72 to 95% after treatment (22).

In another study evaluating oxygen therapy on induced lung injury pigs exposed to phosgene (5), it was mentioned that oxygen is beneficial, with improved arterial oxygen saturation, survival, shunt fraction, and reduced lung wet weight. Furthermore, oxygen therapy can improve arterial oxygen partial pressure. The authors suggest delaying the treatment of P-ALI with inspired oxygen until signs or symptoms of hypoxia become apparent or arterial blood oxygenation decreases. However, it was reported that oxygen therapy can lead to hyper-oxygenation and result in harmful effects (5).

Empirical initiation of antibiotics is discouraged, and they should be reserved for cases where there is clinical evidence of pneumonia or bronchitis (14). Corticosteroid (methylprednisolone/ 125 mg four times daily) was administrated in a case report study after 1 hour of phosgene exposure with complaints of a sore throat (21); however, it was reported that the role of steroids remains controversial (18). Generally, there is not strong evidence for antibiotics and corticosteroids as treatment options for phosgene exposure.

Similar to other ALIs, for phosgene-exposed patients who have difficulty breathing on their own, non-invasive mechanical ventilation is used to help them recover from phosgene exposure. Endotracheal intubation and invasive mechanical ventilation are used in severe cases for artificial respiration, while noninvasive ventilation and supportive therapy help patients breathe comfortably. Suctioning of tracheal secretions and pulmonary oedema fluid is also a crucial component of supportive therapy (20).

Discussion

This study reviewed systematically 13 studies on the mechanism, clinical symptoms, and treatment of phosgene exposure.

Previous studies (12, 13, 30-34) outline the intricate mechanisms of P-ALI, emphasizing the role of pulmonary oedema, inflammation, and oxidative stress. Phosgene swiftly interacts with the alveolar surfactant, depleting it and reacting with tissue components, impairing the plasma membrane and causing the destruction of the pulmonary blood-gas barrier. This leads to the release of inflammatory mediators and ROS, intensifying alveolar capillary permeability and exacerbating pulmonary oedema. Neurogenic pulmonary oedema, induced by phosgene's impact on vagal C-fibers, contributes to P-ALI. Additionally, the carbonyl group in phosgene activates various pathways, triggering inflammation. The NLRP3 inflammasome is activated, further exacerbating inflammation. Overall, anti-inflammatory and antioxidant therapies emerge as potential strategies for treating or preventing P-ALI (35).

The findings showed that inhalation is the primary route of exposure (14-21, 27), except a single case study (21) reported the main exposure from dermal and ocular contact. Initial signs and symptoms range from mild to severe and can include respiratory, cardiac, skin, eye, digestive, and other symptoms. The most common late signs and symptoms reported were dyspnea, cough, audible wheezing, and decreased oxygen saturation with the development of diffuse pulmonary oedema. Inflammation and oxidative stress are the most important parameters in the mechanisms of sub-lethal phosgene damage. Inhalation of phosgene is a significant health hazard, as reported in a short letter study (9). Furthermore, an animal study performed by Pauluhn declared that greyish and slightly swollen lungs, fluid accumulation, and pulmonary haemorrhages were observed during post-mortem examination of rats who had died due to acute lung oedema after phosgene inhaling (8). The studies recommended various treatment options for phosgene exposure, encompassing bronchodilators and expectorants (9, 31, 36, 37), along with supportive measures like oxygen therapy and mechanical ventilation (5).

One strength of this systematic review is its comprehensive analysis of multiple studies on the symptoms/signs and treatments of phosgene exposure, providing an extensive overview of the subject. Another strength is the clear classification of clinical manifestations into categories, making it easier to understand the various symptoms/signs associated with phosgene exposure. However, a limitation

of this systematic review is the limited number of available studies, with only 13 studies analyzed. Additionally, the studies analyzed in this systematic review have a range of methodologies, including some being observational studies and others being case reports and case series. This diversity could impact the overall validity of the results and limit the generalizability of the findings. Further research is needed to determine the efficacy of these treatments in different populations and identify potential adverse effects. Additionally, more research is necessary to assess the effectiveness of treatments in reducing the long-term effects of phosgene exposure.

Conclusion

Phosgene is a respiratory toxic agent, and individuals poisoned by it may exhibit a range of symptoms, from being asymptomatic to experiencing pulmonary oedema. Understanding the clinical manifestations and treatments of phosgene exposure is crucial to minimizing harmful health effects. Based on the results from the current systematic review, bronchodilators can be used to relieve symptoms of bronchoconstriction caused by phosgene. In addition, the administration of oxygen therapy is a crucial intervention to replenish oxygen levels and enhance respiratory function in cases of hypoxemia. Moreover, non-invasive mechanical ventilation can be helpful for patients who have difficulty breathing due to phosgene exposure. Endotracheal intubation and invasive mechanical ventilation are employed in severe cases to provide artificial respiration. Essential elements of supportive therapy also include the removal of tracheal secretions and pulmonary oedema fluid through suctioning.

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Authors' Contributions

A.A., M.Gh.; Conceptualization and Data curation. A.A., Y.H.N.; Investigation. A.A., M.R.P.; Wrote the original draft. Y.H.N, M.R.P., M.Gh.; Wrote, Reviewed, and Edited the manuscript. All authors read and approved the final manuscript.

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