Chlorine Gas Inhalation

Human Clinical Evidence of Toxicity and Experience in Animal Models

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Humans can come into contact with chlorine gas during short-term, high-level exposures due to traffic or rail accidents, spills, or other disasters. By contrast, workplace and public (swimming pools, etc.) exposures are more frequently long-term, low-level exposures, occasionally punctuated by unintentional transient increases. Acute exposures can result in symptoms of acute airway obstruction including wheezing, cough, chest tightness, and/or dyspnea. These findings are fairly nonspecific, and might be present after exposures to a number of inhaled chemical irritants. Clinical signs, including hypoxemia, wheezes, rales, and/or abnormal chest radiographs may be present. More severely affected individuals may suffer acute lung injury (ALI) and/or acute respiratory distress syndrome (ARDS). Up to 1% of exposed individuals die. Humidified oxygen and inhaled β -adrenergic agents are appropriate therapies for victims with respiratory symptoms while assessments are underway. Inhaled bicarbonate and systemic or inhaled glucocorticoids also have been reported anecdotally to be beneficial. Chronic sequelae may include increased airways reactivity, which tends to diminish over time. Airways hyperreactivity may be more of a problem among those survivors that are older, have smoked, and/or have pre-existing chronic lung disease. Individuals suffering from irritant-induced asthma (IIA) due to workplace exposures to chlorine also tend to have similar characteristics, such as airways hyperresponsiveness to methacholine, and to be older and to have smoked. Other workplace studies, however, have indicated that workers exposed to chlorine dioxide/sulfur dioxide have tended to have increased risk for chronic bronchitis and/or recurrent wheezing attacks (one or more episodes) but not asthma, while those exposed to ozone have a greater incidence of asthma. Specific biomarkers for acute and chronic exposures to chlorine gas are currently lacking. Animal models for chlorine gas inhalation have demonstrated evidence of oxidative injury and inflammation. Early epithelial injury, airways hyperresponsiveness, and airway remodeling, likely diminishing over time, have been shown. As in humans, ALI/ARDS can occur, becoming more likely when the upper airways are bypassed. Inhalation models of chlorine toxicity provide unique opportunities for testing potential pharmacologic rescue agents.

Keywords: chlorine; human; lung; toxicity; oxidant; antioxidant

Chlorine is a highly used chemical in industry and society. Human exposures to toxic levels of chlorine are generally accidental. Because release of high levels of chlorine is virtually always unintentional, dosimetric data regarding these exposures is often

not available. Likewise, and for similar reasons, victims of such exposures are usually empirically and/or inconsistently treated. In cases in which a type of treatment has been evaluated, in general, such studies have been uncontrolled. In addition, if and when such exposures and treatments have been reported, these reports have usually been anecdotal. Due to the emergent nature of such treatment, appropriate pulmonary physiology evaluations often have not been performed in the acute phase, nor is such testing always conducted during the chronic phase in follow-up. Pulmonary function measurements preceding exposure of the involved patient also are most often unavailable. Further, in cases in which such exposures have resulted in fatality, autopsy and lung histopathology have not consistently been performed or reported, and in nonfatal cases, lung biopsies are rarely performed.

Chlorine inhalation toxicity can occur during routine attendance at swimming pools, and in higher-level exposures at swimming pools when accidents occur with systems used for water purification (1, 2), during military exposures, following transportation accidents, upon industrial exposure, with misuse of domestic cleaners, and, more recently, as a result of chemical terrorism. The modern use of bleach combined with HCl in developing or developed societies has led to a spectrum of abnormalities from reactive airways dysfunction syndrome (RADS) to adult respiratory distress syndrome (ARDS; acute lung injury, ALI) with fatality (3). Thus, the forms of chlorine involved in respiratory toxicity are not limited to chlorine gas (Figure 1), but also can include hypochlorous acid, chlorine dioxide, and chloramine. In fact, since chlorine gas is moderately water soluble, it can form hypochlorous acid and hydrochloric acid as it dissolves into airway surface liquid when contacting mucosal surfaces and airways (Figure 2). Although the exact mechanism of epithelial damage is unknown, oxidative injury is likely involved, as Cl_2 gas can combine with reactive oxygen species and other airway fluid constituents to form a variety of highly reactive oxidants (4). Direct oxidative injury to the epithelium may occur immediately with exposure to Cl_2 , but further damage to the epithelium may occur with migration and activation of inflammatory cells such as neutrophils within the airway epithelium, with the subsequent release of oxidants and proteolytic enzymes. Through these mechanisms, chlorine exposure can result in injury not only to the lower airways, but also to the eyes, skin, and upper airways. The airway is especially affected from the nose to the level of the bronchi (5). Repair of the airway epithelium following Cl_2 -induced injury may not restore normal structure and function, as cases of subepithelial fibrosis, mucous hyperplasia, and nonspecific airway hyperresponsiveness have been reported after recovery from Cl_2 injury (6, 7). Repeated exposure to chlorine in the pool has been postulated to be a significant risk factor for an excess of asthma among swimmers (8). In atopic adolescents the risk factor of allergic rhinitis and asthma appear to be dose-dependently augmented by chlorinated swimming pool attendance (9).

Limited information is available regarding the time course of injury and repair of the epithelium after acute Cl_2 gas exposure. Bronchial biopsies from humans have shown

(Received in original form January 20, 2010; accepted in final form March 24, 2010)

The research is supported by the CounterACT Program, National Institutes of Health Office of the Director, and the National Institutes of Environmental Health Sciences, Grant Number U54 ES015678.

Also supported by National Institutes of Health Grant NS058081 (to J.G.M. and C.W.W.).

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Proc Am Thorac Soc Vol 7. pp 257–263, 2010

DOI: 10.1513/pats.201001-008SM

Internet address: www.atsjournals.org

also could be due to release of vasoactive mediators such as endothelin, and/or reaction of chlorine, HOCl, or their metabolites with nitric oxide or its metabolites. Indeed, some studies in animal models indicate that elevated pulmonary vascular resistance and diminished cardiac output follows a decline in lung compliance (15). Those surviving such accidents also may have a varied presentation.

CLINICAL PRESENTATION IN ACUTE CHLORINE INHALATION

Among those presenting to the emergency department after the South Carolina accident, the most common clinical finding was wheezing. This was present in 67% of patients (42 of 63) on initial presentation. This resolved within hours in 13 of these 42 individuals. In the remaining 29 patients, wheezing persisted for at least several hours into the hospitalization. However, in another 17% of patients (11 of 63), wheezing was present only after hospitalization progressed, being absent on the initial evaluation in the emergency department. Overall, 84% of patients showed wheezing at some time during their hospital course. By contrast, cough was present in only 37% of patients during the first day of hospitalization. These findings are not specific to chlorine and likely could be found after inhalation of many types of chemical irritants.

Rales or crackles, potentially an indicator of pneumonitis, pulmonary edema, ALI/ARDS, and/or atelectasis, was present in 50% of patients overall on the first day of evaluation, being present only on initial evaluation in 11% (7 of 63).

Of interest also are additional studies performed in relation to other chlorine accidents. Jones and coworkers reported on the outcomes of a Youngstown, Florida train accident in 1978, following up patients for as long as 6 years (16). Initial follow-up was done 3 weeks after the accident. Notably, results from eight persons are excluded, as these individuals died during the acute exposure. Morning cough was noted more frequently among ex- and never-smokers that were closer to the spill at the time it occurred. Among those hospitalized, regardless of smoking status, chest tightness was more prevalent than among those not admitted to hospital. Increased phlegm production also was slightly more prevalent among those ex- and never-smokers. Given that morning cough and sputum production are so prevalent among smokers, it is possible that such symptoms would not be perceived as a change in symptoms among the smokers. Among all individuals close to the spill, wheezing, and shortness of breath with wheezing, were reported as slightly more prevalent than among those farther from the spill (16).

PULMONARY FUNCTION EFFECTS OF CHLORINE INHALATION

There are relatively few good studies of lung function after transportation or industrial accident-related chlorine exposure. Pulmonary function abnormalities that can occur within 1 day of chlorine exposures include airflow obstruction and air trapping (11). In follow-up 12 years after such accidental exposures, these patients tended to show persistent airflow obstruction. By contrast, air trapping was generally resolved, often with this abnormality being replaced by volume loss. In fact, by this stage, about two-thirds of such individuals had lung residual volumes that were less than 80% predicted ($P < 0.001$) (17). In addition, a high level of airways hyperreactivity to methacholine also persisted in this population, with 38% of victims showing greater than 15% decline in FEV₁ in response to methacholine (17). In this series, the patients with residual airways reactivity to methacholine were (1) older ($P < 0.004$),

(2) had more marked airflow limitation ($P = 0.03$), and (3) had more air trapping initially ($P = 0.03$).

In another study of patients with accidental chlorine exposure, individuals immediately after exposure (e.g., within 24 h) showed airflow limitation (10 of 19 exposed individuals) and increased residual volumes ($141 \pm 97\%$ predicted values) (18). By contrast, pulmonary function abnormalities in these individuals 2 years after exposure included airflow limitation in only 3 of 11 patients, and, of these, 2 were smokers. In addition, the residual volume measured in this group was no longer elevated ($90 \pm 5\%$) (18). Additional studies have shown that patients with a previous history of smoking, wheezing, asthma, and/or increased airway reactivity are at greater risk for more persistent airways obstruction after chlorine inhalation (19, 20). Thus, the damage from smoking, or from other pre-existing pulmonary conditions, and that due to chlorine exposure could be additive, potentiative, or synergistic.

On the other hand, not all studies have reported an enduring effect of chlorine inhalation accidents on pulmonary function among survivors. For example, Jones and colleagues (16) reported that there was an absence of important or consistent differences in pulmonary function 3 weeks after exposure in persons according to severity of acute injury or distance from the spill. Thus, the early symptoms present in some of those affected were not explicable by lung function testing abnormalities. In addition, they reported a "lack of evidence for continuing adverse effects" on lung function over the 6-year follow-up of these survivors. Specifically, they noted that there was "no detectable difference in lung function relating to distance or apparent severity of injury." And in 60 adults tested repeatedly over 6 years, the longitudinal changes showed expected differences related to smoking but not related to distance or severity of injury (16). Thus, these investigators asserted that there is a "favorable long-term prognosis after acute chlorine injury."

In another study of patients exposed to fairly high levels of chlorine, pulmonary function studies were done at 3 and 7 years after exposure. These studies were done in individuals exposed in another rail accident in Morganza, Louisiana in 1961, in which 1 (a child) died, 11 were hospitalized more than 2 weeks, and over 100 were symptomatic initially. In general, the studies were remarkable for how nearly normal these studies were in many of the victims. In a small study of twelve surviving children and adults, patients were "essentially asymptomatic" and with normal chest films. In addition, they reported that lung volume abnormalities, when they occurred, "could be accounted for by factors other than chlorine exposure" and that lung mechanics, gas exchange, and blood gases were also normal or abnormal due to other factors (21).

The results of workplace exposure to chlorine are even more complex than that related to single accidental exposures. Although acute toxicity of chlorine is usually thought to occur primarily with short-term, high-level exposures (traffic accidents, spills, and other accidents or disasters), acute, higher-level exposures also can occur, for example, in the workplace. However, occupational and public exposures can often be primarily longer-term and may involve lower levels of chlorine. Recently, Malo and coworkers (22) reported a series of patients with irritant-induced asthma (IIA) (23), previously referred to as RADS. This is one subgroup of occupational asthma (OA). The majority of participants in the study had had known exposures to chlorine (57%), whereas a minority were exposed to other chemical agents. All of the participants had been compensated since 1988 for IIA that developed after an inhalation accident at work. The majority were men. Diagnosis of IIA required that symptoms developed within 24 hours after the accident, that there was no history of asthma or any other

chronic obstructive lung disease, and that there be either bronchial hyperresponsiveness (85% of participants) or "significant airway obstruction" ($FEV_1 < 1.5$ L; 15% of participants). Patients had a mean duration of symptoms of 13 or more years, with a minimum duration of 4 years. Almost all of them continued to have asthma symptoms, and a third of them were using inhaled corticosteroids. A third of them continued to smoke. Performance on spirometry continued to be low, averaging 70% for FEV_1 and FVC both at diagnosis and follow-up. Of those given repeat methacholine challenge, 74% (17 of 23) had ongoing airway hyperreactivity. The remainder ($n = 12$) within the cohort of 35 patients could not undergo methacholine challenge because of FEV_1 less than 1.5 L. Of these, two-thirds had an improvement in FEV_1 greater than 11% with inhalation of bronchodilator. The type of chemical exposure (chlorine versus chemical[s] other than chlorine) did not influence outcome as assessed by pulmonary function, markers of inflammation in induced sputum, psychological testing, and need for care in an emergency setting. Those who showed improvement in pulmonary function tended to be younger and to have had higher FEV_1 and PC_{20} values initially. Perhaps not surprisingly, being a smoker at the time of the original accident was associated with a diminished performance on pulmonary function at follow-up, potentially indicating a combined effect of smoking and chemical exposure, as suggested in previous studies. For example, Gautrin and colleagues showed prospectively that the number of "puffs" (accidental occupational chlorine exposures resulting in the employee seeking emergency medical attention) and smoking showed an additive effect in causing airflow limitation and increased bronchial reactivity to methacholine over time (24). Together, these studies tend to indicate that there are likely to be some highly susceptible or vulnerable subsets of patients, both among smokers and nonsmokers, who may suffer excessively severe problems with ongoing airflow limitation and airways hyperreactivity associated with prior inhalation of chlorine or other toxic gases and/or chemicals. Again, a somewhat different interpretation of the results could be that cigarette smoke-related airways damage is additive, potentiative, or synergistic with that of chlorine exposure. Such interactions may be more apparent with repeated episodes of occupational exposure. In addition, the recent study of Malo and coworkers indicates that some of these patients may have biomarkers of inflammation persisting for years in their sputum, including eosinophilia, neutrophilia, and/or elevation of certain classes of matrix metalloproteinases (MMPs). Given the diagnostic approaches taken, it is also conceivable that some of the patients in this series may have had bronchiolitis obliterans (BO) rather than, or in addition to, IIA.

Additional studies have indicated that the type of toxic occupational exposure also may impact the disease phenotype present. For example, Henneberger and colleagues (25) showed that, among Swedish paper mill/bleachery workers, exposures to ozone as a bleaching agent caused differing symptoms and disease phenotypes than exposures to chlorine dioxide/sulfur dioxide for this purpose. Workers that had been exposed to both types of bleaching agents showed elevated hazard ratios for the three principal presentations monitored: physician-diagnosed asthma; acute wheezing attacks (one or more episodes); and chronic bronchitis (chronic cough with phlegm). Those who had peak exposures only to ozone had elevated hazard ratios for asthma (6.5) and acute wheezing attacks (3.3), but without elevated hazard ratio for chronic bronchitis. Ozone exposures were substantial (> 900 ppb on 6 of 366 monitoring days; > 300 ppb on more than a third of monitoring days). By contrast to workplace ozone exposures, those exposed to

chlorine dioxide and sulfur dioxide showed elevated hazard ratios for chronic bronchitis (22.9) and wheezing attacks (7.5) but not for asthma. It would be of future interest to know the status of biomarkers of inflammation in sputum and/or bronchoalveolar lavage in patients such as these as well.

CLINICAL BIOMARKERS OF DISEASE IN THE ACUTE SETTING

Although several of the outcomes of acute chlorine inhalation are predictable, none appear to be specific for chlorine. Hypoxemia is a common finding. In studies of victims of chlorine inhalation following a 2005 South Carolina train derailment accident, a low Pa_{O_2}/Fi_{O_2} ratio was found in 58% of those that survived long enough for emergency evaluation (pulse oximetry and/or arterial blood gas analysis). In addition, an abnormal chest radiograph was found in 57% of these individuals, with 75% of those showing abnormalities within the first day after exposure. Finally, a diminished peak flow rate, identified either on spirometry or by peak flow meter, was a common finding (12). Specific biochemical markers to identify chlorine inhalation victims and to estimate inhaled dose would be useful for future studies of both accidental and occupational exposures. Some that might be worthy of further exploration would include surfactant proteins (SP-A, SP-D, etc.), Clara cell secretory proteins, and chlorotyrosine residues in protein, any of which might appear in various compartments including blood plasma, sputum, bronchoalveolar lavage fluid (BALF), and/or lung tissue. Although chlorotyrosine might be more specific to chlorine-related injury, it too could be produced via inflammation in a variety of settings.

TREATMENT FOR CHLORINE RESPIRATORY TOXICITY

Treatment for chlorine inhalation in humans is largely supportive. Current treatments for chlorine inhalation toxicity are based on reported experience in the literature, much of which is anecdotal, a few controlled human studies, and additional treatment studies in large and small animal models. Importantly, supplemental *humidified* oxygen is appropriate for *all* victims until proper assessment of oxygenation can be performed. In addition, use of inhaled β -adrenergic agents is also appropriate for patients who show clinical signs of airway obstruction such as wheezing, diminished breath sounds, increased work of breathing, unmitigated cough, or other signs of respiratory distress (26). Although there have been some studies of use of inhaled bicarbonate anecdotally reporting therapeutic benefits, these studies have been either (1) uncontrolled (27) or (2) unable to demonstrate therapeutic benefit by pulmonary physiology (28). Nonetheless, the approach appears safe (27). Finally, a limited number of uncontrolled studies have also indicated possible benefits of treatment with glucocorticoids, including both systemic corticosteroid (29) and inhaled agents such as budesonide (30). It is difficult to know the extent of potential benefit of these therapies on long-term outcomes.

ANIMAL MODELS OF CHLORINE-INDUCED LUNG INJURY

The acute effects of chlorine have been studied in a number of animal models. The solubility of chlorine is such that there is an effective scrubbing of gas within the proximal airways leading to a gradient of damage from the nasal passages to the peripheral lung (31). This contrasts with ozone, which penetrates more deeply into the lung. Therefore exposure to low concentrations of chlorine causes preferential damage to the large airways, and

alveolar damage requires exposure to high concentrations of gas. Such exposures will necessarily cause concurrent extensive airway damage. High concentrations of chlorine (800 ppm for 5 min) cause mixed airway and alveolar damage. There is an acute airway inflammatory response and an increase in responsiveness to methacholine challenge (32). The neutrophil chemoattractant chemokine and IL-8 ortholog KC is increased by 6 hours after exposure to chlorine (33) and may account in part for the rapid influx of neutrophils. There may also be a strain dependence of sensitivity to chlorine injury, although this has not been extensively studied as has been done for ozone-exposed mice (34). These changes are consistent with the concept of irritant-induced asthma, although in the model systems the animals recover from the injury and there is not generally a persistence of the functional abnormalities beyond 10 days after exposure. However, the presence of an increase in airway smooth muscle mass has been noted at this time point, suggesting the possibility of a more protracted course of airway remodeling (32).

A single acute exposure of Sprague Dawley rats to chlorine causes airway lesions with desquamation of the epithelium acutely and fibrosis more remotely. Increase in airway smooth muscle mass has also been described to persist over several months in some animals, and it has been associated also with persistent airway hyperresponsiveness (35, 36). Whether the remodeling of the airway smooth muscle accounts for the hyperresponsiveness to methacholine has not been established. The histologic evidence of alveolar edema is transient, diminishing within hours (35). Exposure studies in the mouse have also shown an acute inflammatory response with a predominance of neutrophils and airway hyperresponsiveness to methacholine (37). The changes resolve within 10 days (32). Airway hyperresponsiveness seems to be less consistently induced following exposure to very high concentrations of chlorine (800 ppm for 5 min), and 5 days after the exposure there is a strong trend for airway smooth muscle mass to be reduced, suggesting that damage under these circumstances may extend below the epithelial layer to the muscle (32). However, there is recovery of this effect also by 10 days.

There is strong evidence that much of the chlorine-induced damage to the airways is oxidative in nature. Evidence is derived from the finding of markers of oxidative stress and from the amelioration of the abnormalities by low-molecular-weight antioxidants. Exposure to 400 ppm for 5 minutes causes carbonylation of lung proteins and an increase in nitrotyrosine residues (37). Inhibition of iNOS abrogates the increase in airway hyperresponsiveness (37). Exposure of rats to Cl₂ gas (400 ppm) for 30 minutes led to functional changes as early as 1 hour after exposure with arterial hypoxemia, respiratory acidosis, and protein leak into BALF. There was histologic evidence of airway and alveolar epithelial damage. Decreases of ascorbate (AA) and reduced glutathione (GSH) were also detected in both BALF and lung tissues for up to 24 hours. Systemic administration of ascorbic acid, deferoxamine, and N-acetyl-L-cysteine before exposure to 184 ppm Cl₂ normalized levels of AA, and reduced BALF albumin. Blood gas abnormalities were also attenuated by prophylactic administration of the low-molecular-weight antioxidants (38). Corticosteroids have also been shown to diminish the effects of chlorine toxicity in the rat (39).

$\gamma\delta$ -T cells have been found to have trophic properties for intestinal and cutaneous epithelial cells (40, 41). There is also evidence that they may have a role in the airways, although they are less numerous there than in the aforementioned tissues. It appears that chlorine causes more airway injury in $\gamma\delta$ -T cell-deficient mice (42). Following chlorine exposure, the numbers of epithelial cells in the BALF of mice that are

deficient in $\gamma\delta$ -T cell receptor is greater than in wild-type animals (42). The inflammatory response to chlorine exposure is delayed in the $\gamma\delta^{-/-}$ mice, and the change in airway responsiveness to methacholine is also diminished. This suggests that the inflammatory response to chlorine exposure may contribute to the increase in responsiveness in addition to the more direct effects mediated by epithelial cell damage.

The exposure of isolated blood-perfused rabbit lung to 500 ppm of chlorine for 10 minutes leads to an increase in microvascular permeability, reflected in an increase in fluid filtration rate and filtration coefficient (43). In intact pigs there is a rise in circulating endothelin-1 levels after chlorine exposure, and the increase in pulmonary vascular resistance associated with the exposure is reversed by an endothelin antagonist (44). Perhaps such treatment would be useful in human subjects with acute lung injury, given the cardiomegaly that is observed in such patients.

A variety of small and large animal models of chlorine injury has been studied, providing insights into the human condition. A range of concentrations and durations of exposure have been employed. It is difficult to compare these exposures to those experienced by human subjects for a variety of reasons. It is likely that different species will demonstrate differences in sensitivity to oxidant injury. Furthermore, the proportionate or relative olfactory epithelial surface area of the upper airways in small animals such as the rat or mouse is very large relative to lung surface area as compared with human subjects. Specifically, rodents have a very large olfactory surface area (50% of nasal cavity in rat) in a very susceptible location, whereas humans have, relatively speaking, a much smaller olfactory surface area (5% of nasal cavity) in a less susceptible dorsal posterior location (45). The removal/absorption of chlorine within the upper airways will modify the toxicity to the lower airways. Alveolar injury requires exposure to high concentrations of chlorine because of the solubility of the gas and due to its rapid removal/absorption within the upper airways at lower concentrations. Alveolar damage will occur at lower concentrations of chlorine if the upper airways are bypassed, as has been the case in some experimental models of lung injury. However, even in cases in which alveolar damage is induced, the physiological impairment is potentially substantially attributable to concomitant airway damage. This is consistent with the clinical presentation of exposed subjects, with a high prevalence of signs of obstructive impairment.

CONCLUSIONS

In summary, chlorine exposure results in a direct chemical toxicity to the airways that is potentiated by the ensuing inflammatory response. Oxidative damage to airways may result during either stage of illness. Acute airways obstruction followed by airways remodeling and/or airways hyperresponsiveness may be seen following chlorine exposures both in animal models and in humans. The results of human chlorine inhalation may range from acute overwhelming intoxication with acute lung injury and/or death to intermittent or repeated accidental or unintentional occupational exposure. The latter tends to result in greatly increased hazard ratios for chronic bronchitis or isolated wheezing attacks, but with less likelihood of development of clinical asthma than occurs in those with occupational exposures to ozone. Cigarette smokers may be particularly vulnerable to these results of occupational chlorine inhalation exposures. Alternatively, lung damage due to chlorine and that due to smoking could be additive or synergistic. Chronic low-level exposures to chlorine also may be associated with considerably greater odds ratios for having or developing asthma, hay

fever, and allergic rhinitis in vulnerable atopic populations exposed to chlorinated, but not copper-silver-treated, swimming pools (9). There is no evidence that youth protects against such insults, or that it necessarily carries excessive risk of poor outcomes. Thus, while those fortunate to survive acute severe chlorine inhalation may eventually be left without pulmonary disability, a pattern of findings indicates that specific vulnerable populations of individuals such as smokers and atopic individuals may suffer from chronic respiratory disorders resulting from less profound unintentional exposures. At present, recommended treatment of persons suffering from acute accidental chlorine inhalation exposures is supportive and symptomatic. Development of new therapies, with trials in appropriate models, could lead to improvements in care of these individuals.

Conflict of Interest Statement: C.W.W. received grant support from the National Institutes of Health (NIH) (more than \$100,001) and his spouse/life partner received grant support from the NIH (\$50,001–\$100,000). J.G.M. received lecture fees from Merck and Altana (up to \$1,000). He received grant support from Merck (\$50,001–\$100,000), the NIH, and CIHR (more than \$100,001).

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