# Outcome of occupational asthma

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**Purpose of review**

Occupational asthma is often associated with serious work and financial consequences. Correct management of occupational asthma must be based on a good knowledge of the natural history of the disease and of its prognostic factors.

**Recent findings**

Longitudinal studies have demonstrated that improvement of symptoms and airway hyperresponsiveness may be prolonged after cessation of exposure. Severity of asthma at diagnosis is the best predictor of clinical symptoms and functional impairment at follow-up. The molecular weight of the causal agent does not seem to be a prognostic factor. Airway inflammation is associated with persistence of symptoms and airway hyperresponsiveness after cessation of exposure. Reduction of exposure has proved to be effective in improvement of latex-induced asthma.

**Summary**

Further studies are needed to investigate the prognostic value of sputum eosinophils and neutrophils, and to determine whether some specific agents are associated with a better prognosis than others.

**Keywords**

airway inflammation, asthma outcome, occupational asthma, socioeconomic outcome

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**Abbreviations**

| | |
|---|---|
| **NSBH** | nonspecific bronchial hyperresponsiveness |
| **$PC_{20}$** | provocative concentration of methacholine causing a 20% fall in $FEV_1$ |
| **$PD_{20}$** | provocative dose of methacholine causing a 20% fall in $FEV_1$ |

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## Introduction

About one in ten cases of adult asthma are associated with occupational factors [1], which makes occupational asthma one of the most frequent occupational respiratory diseases in industrialized countries. The outcome of occupational asthma differs considerably according to persistence or avoidance of exposure after onset of symptoms.

The present review focuses on new data concerning the patterns of improvement of clinical and functional parameters after cessation of exposure, the prognostic factors, socioeconomic outcome of occupational asthma, and outcome of sensitizer-induced asthma in patients who remain in the same job after reduction of exposure or treatment by inhaled steroids.

## Outcome of sensitizer-induced occupational asthma in patients removed from exposure

Complete avoidance of exposure is associated with improvement in asthma symptoms and functional parameters, although symptoms and nonspecific bronchial hyperresponsiveness (NSBH) persist in approximately 70% of cases [2,3].

### Patterns of improvement of clinical and functional parameters

In a series of cases of occupational asthma due to snow crab, Malo *et al.* [4] observed a plateau of improvement of spirometry 1 year after cessation of exposure, whereas provocative concentration of methacholine causing a 20% fall in $FEV_1$ ($PC_{20}$) seemed to plateau after 2 years [4]. Several years later, however, in a study conducted in patients with occupational asthma caused by various agents, the same group of investigators found that those removed from exposure for 5 years or more had a more favorable outcome than those seen at a shorter interval [5]. A recent study conducted by Malo and Ghezzo [6••] in 80 patients with occupational asthma due to various agents, confirmed by specific inhalation challenge, showed that the NSBH recovery rate, although faster during the first 2.5 years after exposure, continued thereafter at a threefold lower rate on average.

Two other recent studies confirmed that improvement of symptoms and NSBH can continue over several years after cessation of exposure. Padoan *et al.* [7••] reported the results of a follow-up study of 87 cases of occupational asthma induced by toluene diisocyanate, diagnosed by inhalation challenge. Seventy-four of these 87 patients

had been removed from exposure – 44 for less than 10 years and 30 for more than 10 years. At follow-up examination, respiratory symptoms persisted in 75% of patients removed from exposure for less than 10 years and in 60% of those removed from exposure for more than 10 years. The degree of airway responsiveness was also slightly lower in patients removed from exposure for more than 10 years. Maghni *et al.* [8••] assessed 133 patients with occupational asthma due to various causal agents at a mean interval of 8.7 years after cessation of exposure. Three groups were defined according to clinical status at follow-up: cured (normalization of $PC_{20}$), improved, or not improved; 27% were cured, 43% were improved, and 30% were not improved. The time since diagnosis was significantly different in the three groups: 9.8 years in the cured, 7.6 in the improved, and 6.8 in the not improved.

### Prognostic factors

The main prognosis factors identified to date are the duration of exposure after onset of asthma symptoms and the severity of asthma at the time of diagnosis. Conflicting findings have been reported concerning the total duration of exposure, the type of reaction during specific inhalation challenge (early, dual, or late), and the type of causal agent (high-molecular weight agent or low-molecular weight agent).

The studies by Padoan *et al.* [7••] and Maghni *et al.* [8••] provided new data concerning the prognostic factors of occupational asthma. These two studies are important because of the large study population, the accuracy of the diagnostic methods, and the long follow-up. Padoan *et al.* [7••] performed stepwise logistic regression to evaluate the effects of potential factors. In agreement with previous findings, they found that level of airway responsiveness to methacholine, at the time of diagnosis, is a predictor of persistence of airway responsiveness. In all models, provocative dose of methacholine causing a 20% fall in $FEV_1$ ($PD_{20}$) was a significant predictor of $PD_{20}$ at follow-up (a lower degree of NSBH at diagnosis was associated with a lower risk of hyperresponsiveness at follow-up). The duration of exposure (total exposure at work) and ongoing treatment with inhaled steroids were predictors of $PD_{20}$ at follow-up, but with only borderline significance (ongoing treatment with inhaled steroids being a marker of better outcome). Multiple regression analysis showed that follow-up $FEV_1$, and forced vital capacity values could be predicted from those at diagnosis. In the study by Maghni *et al.* [8••], logistic regressions were used to examine factors associated with functional outcomes. The authors showed the baseline $PC_{20}$ and time since diagnosis were significantly associated with $PC_{20}$ values at follow-up. Unlike previous findings reported by the same team, showing a better outcome for patients with occupational asthma due to low-molecular weight agents rather than due to high-molecular weight agents [5], the authors did not observe any significant differences of outcome according to the nature of the causal agent.

### Prognostic significance of airway inflammation

Despite cessation of exposure, a majority of patients with occupational asthma remain symptomatic with persistence of NSBH. Airway inflammation and structural changes ('remodelling') in the airways are probably important for persistence of occupational asthma. However, the role of ongoing inflammation and various structural airway changes is not yet clear [9•].

Over recent years, induced sputum analysis has been shown to be a reproducible, valid, and noninvasive method to study airway inflammation [10•]. Maghni *et al.* [8••] hypothesized that persistence of asthma after cessation of exposure could be explained by the presence of airway inflammation. They found that one-third of patients with persistent asthma had significant eosinophilia and neutrophilia, a rate twofold higher than that observed in those who were cured or improved. Levels of interleukin-8 and neutrophil-derived myeloperoxidase were also significantly higher in sputum from patients with no improvement.

These results show that absence of improvement of airway responsiveness in patients with occupational asthma after removal from exposure is associated with airway inflammation at follow-up. However, as sputum was not examined before cessation of exposure, the data reported by Maghni *et al.* do not characterize the baseline severity of inflammation and do not indicate whether or not patients with persistent inflammation actually improved during follow-up. As underlined by Maestrelli [11•], the ideal study design to prospectively assess the consequences of occupational asthma would be to include measurements of airway inflammation and lung function before and after removal from exposure to causal agents. Despite these limitations, the study by Maghni *et al.* suggests that airway inflammation is the cause of persistent NSBH and asthma symptoms, which could lead to the development of new treatment strategies.

## Socioeconomic outcome

Several studies conducted in various countries investigating the socioeconomic consequences of occupational asthma have been recently reviewed by Vandenplas *et al.* [12••]. These studies show that occupational asthma is associated with considerable work and financial consequences: 25–38% of patients with occupational asthma suffer prolonged work disruption and 42–78% report a substantial loss of income. Income is particularly affected in those workers who are removed from exposure, as they often lose their jobs. However, even some patients who

keep their jobs are financially affected due to sickness and lack of promotion [13]. Deterioration of the socioeconomic and employment status after cessation of exposure explains why many individuls choose to remain exposed to the offending agent.

## Outcome of occupational asthma in patients with continuous or reduced exposure

Most studies have shown that patients with occupational asthma deteriorate if they continue in the same job [2,3]. Therefore, there is a general consensus that complete and definitive removal is the key to treatment of occupational asthma. In the case of persistence of exposure or reexposure to the causal agent, there is a low but real risk of death due to status asthmaticus. In 2002, a review of the literature identified 10 cases of fatal occupational asthma [14] and another case due to psyllium in a health care worker was reported in 2003 [15]. Even in patients who become asymptomatic with normal bronchial responsiveness after avoidance of exposure, specific bronchial reactivity may persist [16•] and there remains a risk of developing an asthmatic reaction following reexposure to the offending agent. Consequently, complete avoidance of exposure is the most effective treatment of sensitizer-induced asthma and should be strongly recommended to affected workers [9•].

It is not always possible for affected individuals to find alternative employment – it depends on the labor market in the country concerned. Furthermore, patients with occupational asthma become unusually sensitive to nonspecific stimuli such as cold air, dust, or irritants, often present at the workplace. Inadequate compensation in many countries may also contribute to the decision of workers to remain exposed after diagnosis [13]. Reduction of exposure, which can be achieved by relocation to less exposed jobs, improvement in workplace hygiene, use of modified material, and use of personal protective devices, is therefore an alternative that is worth considering.

The long-term health effects of reduction of exposure have been poorly investigated. In a comprehensive review, Vandenplas *et al.* [12••] identified only six studies comparing the long-term outcome of patients with occupational asthma who reduce exposure, with those who completely avoid further exposure. Pooled analysis of these studies indicates that reducing exposure is more frequently associated with persistence of asthma symptoms and persistence of NSBH, and with worsening of asthma than complete removal.

The outcome after reduction of exposure appears to vary according to the causative agent. For instance, it appears to be better for latex-induced asthma than for isocyanate-induced asthma. In a follow-up study of 36 patients with latex-induced asthma investigated after a median follow-up of 56 months, Vandenplas *et al.* [17] found that in the 20 individuals who reduced their exposure, asthma severity and NSBH significantly improved. Similarly, among 19 health care workers with work-related asthma symptoms and documented latex allergy who switched to nonnatural rubber latex gloves, 18 reported resolution of all symptoms despite the fact that 12 out of the 18 continued to work with fellow employees who used powdered nonnatural rubber latex gloves [18•].

## Influence of treatment on outcome

The efficacy of inhaled steroids in the treatment of occupational asthma has been poorly investigated. Improvement in various clinical and functional parameters has been documented in patients with sensitizer-induced occupational asthma treated by inhaled steroids after cessation of exposure [2]. Marabini *et al.* [19•] evaluated the effect of treatment with beclomethasone dipropionate and salmeterol in 10 patients with mild-to-moderate occupational asthma still exposed to the work environment responsible for their disease. After 3 years they observed a nonsignificant deterioration in clinical or functional parameters despite persistence of exposure. However, this study was uncontrolled and the number of patients was small, consequently these results need to be confirmed in larger series.

## Outcome of irritant-induced asthma

Few cohort studies have assessed the outcome of NSBH in occupational asthma induced by massive inhalation of irritant substances. The results of these studies have been analysed by Vandenplas *et al.* [12••]. Taken together, the available studies show that NSBH can continue to improve for up to 3 years following an inhalation accident, which is quite similar to what has been described in patients with immunological occupational asthma.

In firefighters highly exposed to airborne particulates at the World Trade Center site, Banauch *et al.* [20••] demonstrated that predictive factors for persistence of NSBH were exposure intensity and hyperreactivity shortly following collapse.

## Conclusion

Studies published over the last 2 years have improved our knowledge of the outcome of occupational asthma and demonstrate the following main points.

(1) Improvement in symptoms and NSBH after cessation of exposure can occur over several years.
(2) $PC_{20}$ or $PD_{20}$ methacholine at diagnosis seems to be the best predictor of airway responsiveness at follow-up.
(3) The outcome of occupational asthma does not differ according to the molecular weight of the causal agent.

(4) Airway inflammation is associated with persistence of symptoms and NSBH.
(5) Reduction of exposure by appropriate means could represent an acceptable compromise in certain cases, for example, for natural rubber latex sensitization, in individuals who opt to remain in the same job for financial reasons.

Further studies are needed to determine whether some specific agents are associated with a better prognosis than others, and to investigate the prognostic value of markers of inflammation at the time of diagnosis. Usefulness of inhaled steroids in workers not removed from exposure should also be examined further.

## References and recommended reading

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**11** • Maestrelli P. Natural history of adult-onset asthma. Am J Respir Crit Care Med 2004; 169:331–332.
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