Original Article

Occupational Asthma Caused by Quaternary Ammonium Compounds: A Multicenter Cohort Study

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What is already known about this topic? Occupational asthma caused by quaternary ammonium compounds (QACs) has been documented in workers exposed to cleaning and disinfectant products, although the underlying mechanisms remain largely unknown.

What does this article add to our knowledge? This retrospective study demonstrates that asthmatic reactions induced by QACs are associated with increases in nonspecific bronchial hyperresponsiveness and sputum eosinophils that are consistent with a respiratory sensitizing mechanism.

How does this study impact current management guidelines? This report further indicates that exposure to QACs should be considered a potential cause of sensitizer-induced occupational asthma among workers involved in cleaning and disinfection tasks.

BACKGROUND: Quaternary ammonium compounds (QACs) are used extensively for cleaning and disinfection and have been documented in scattered reports as a cause of occupational asthma (OA) through bronchoprovocation tests (BPTs).
OBJECTIVE: To examine the clinical, functional, and inflammatory profile of QAC-induced OA compared with OA caused by other low−molecular weight (LMW) agents.
METHODS: The study was conducted in a retrospective multicenter cohort of 871 subjects with OA ascertained by a positive BPT. Subjects with QAC-induced OA (n = 22) were identified based on a positive BPT to QACs after exclusion of those challenged with cleaning products or disinfectants that contained other potential respiratory sensitizers. They were compared with 289 subjects with OA caused by other LMW agents.
RESULTS: Most subjects with QAC-induced OA were working in the health care sector (n = 14). A twofold or greater increase in the postchallenge level of nonspecific bronchial hyperresponsiveness was recorded in eight of 11 subjects with QAC-induced OA (72.7%) and in 49.7% of those with OA caused by other LMW agents. Although sputum assessment was available in only eight subjects with QAC-induced OA, they showed a significantly greater median (interquartile) increase in sputum eosinophils (18.1% [range, 12.1% to 21.1%]) compared with those with OA caused by other LMW agents (2.0% [range, 0% to 5.2%]; $P < .001$).
CONCLUSIONS: This study indicates that QAC-induced OA is associated with a highly eosinophilic pattern of airway response and provides further evidence supporting the sensitizing potential of QACs. The findings highlight the heterogeneous

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Abbreviations used
BPT- Bronchial provocation test
CAS- Chemical Abstracts Service
CI- Confidence interval
FeNO- Fractional exhaled nitric oxide
FEV_1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
IQR- Interquartile range
LMW- Low−molecular weight
NSBH- Nonspecific bronchial hyperresponsiveness
OA- Occupational asthma
QAC- Quaternary ammonium compound

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Key words: *Asthma; Biocides; Cleaning agents; Occupational disease; Quaternary ammonium compounds*

INTRODUCTION

Quaternary ammonium compounds (QACs) have the generic chemical structure $N(R_1R_2R_3R_4)^+ Cl^-$, in which $R_{1\text{-}4}$ is alkyl or aryl groups with a varying carbon chain length. These compounds are used extensively for cleaning and disinfecting surfaces, instruments, and equipment, especially in health care and food processing facilities, because of their broad-spectrum antimicrobial activity.[1,2] Asthmatic reactions induced by the most widely used QACs, benzalkonium chloride (Chemical Abstracts Service [CAS] 8001-54-5) and didecyldimethylammonium chloride (CAS 7173-51-5), have been documented through bronchial provocation tests (BPTs) in a few case reports[3-5] and limited case series.[6,7] A physician-based notification scheme of work-related asthma in France reported a significant upward trend in incident cases attributed to QACs, from 1.4% of reported cases in 2001 to 8.3% in 2009, mainly in the health and social sectors.[8] Nevertheless, epidemiologic surveys of cleaners either did not address exposure to QACs specifically[9-13] or failed to document an association between asthma and exposure to QACs.[14,15] A notable exception was Gonzalez et al,[16] who found an association between exposure to QACs and increased risk for asthma in a survey of health care workers. Overall, the role of QAC exposure in the development of asthma remains largely unknown and controversial.[17,18]

This study aimed to characterize the clinical, functional, and inflammatory profiles of occupational asthma (OA) caused by QAC ascertained by a positive BPT and to compare these phenotypic patterns with those of OA caused by other low−molecular weight (LMW) agents.

METHODS

Study design and population

This retrospective, observational study was conducted in a cohort of 871 subjects who showed a positive BPT with various occupational agents between January 2006 and December 2018 in six centers participating in the European network for the Phenotyping of Occupational Asthma (E-PHOCAS).[19-22] This analysis was restricted to six E-PHOCAS centers that were selected based on the performance of induced sputum analysis before and after BPT, although this technique was unavailable throughout the whole 2006 to 2018 study period in each center. Recruitment of the population included in this analysis on cleaners' OA is described in Figure 1 and Table E1 of this article's Online Repository at www.jaci-inpractice.org.

The data collection process used by the E-PHOCAS cohort was previously been described elsewhere.[19-22] Briefly, detailed anonymized information on demographic, clinical, occupational, and physiologic characteristics of subjects at the time of the diagnostic evaluation was entered in a standardized Excel (Microsoft Corporation, Redmond, WA) spreadsheet in each participating center. The requested data were retrieved from medical charts in two centers, whereas in the other centers, all or most of the data had been prospectively entered in existing local databases. At the time of data collection, the local investigators were unaware of the specific aims of the analyses that would be subsequently conducted. Important outcomes, such as the results of BPTs, asthma severity, and the level of nonspecific bronchial hyperresponsiveness (NSBH), were interpreted and recoded a posteriori using uniform and validated criteria. The local databases were checked for missing data and inconsistencies by the investigators (OV, CR, and JD), pooled together, and centralized at the Strasbourg University.

Ethics

Approval for this retrospective analysis of anonymized data was obtained from each local institutional review board. The central database at the Strasbourg University was approved by the Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé and the Commission Nationale de l'Informatique et des Libertés.

Identification of asthma induced by QACs

First, subjects with OA caused by cleaning agents were retrieved by screening the recorded occupation and causal agent fields of the E-PHOCAS database. A cleaning agent was defined as any material used for cleaning or disinfecting houses, buildings, health care equipment, or specialized service and industrial facilities, with the exceptions of degreasing metal parts[23] and textile dry cleaning. In case of doubt, further information on job tasks and products used at work were requested from the local investigators. This resulted in the identification of 55 subjects with cleaners' OA.

Occupational asthma caused by QACs was defined by a positive BPT response induced by a QAC alone, in the absence of any other potential respiratory sensitizer. To identify subjects with QAC-induced OA, safety data sheets of cleaning products that elicited positive BPTs were reviewed. The respiratory sensitization potential of their ingredients was assessed using a validated quantitative structure−activity relationship model[23,24] that generates quantitative estimates of the probability that LMW organic agents have respiratory sensitization potential based on their chemical structure (ie, the asthma hazard index) (see Appendix E2 in this article's Online Repository at www.jaci-inpractice.org). Based on this approach, subjects were assigned to one of three categories: (1) positive BPT induced by a single respiratory sensitizing agent (n = 30); (2) positive BPT elicited by challenge exposure to one or more products containing multiple potential sensitizers (n = 21); and (3) positive BPT without an identified sensitizer (n = 4). Potential respiratory sensitizers involved in the 55 subjects with cleaners' asthma are detailed in Table I. The single-sensitizer positive BPTs were induced by QACs in 22 subjects, including

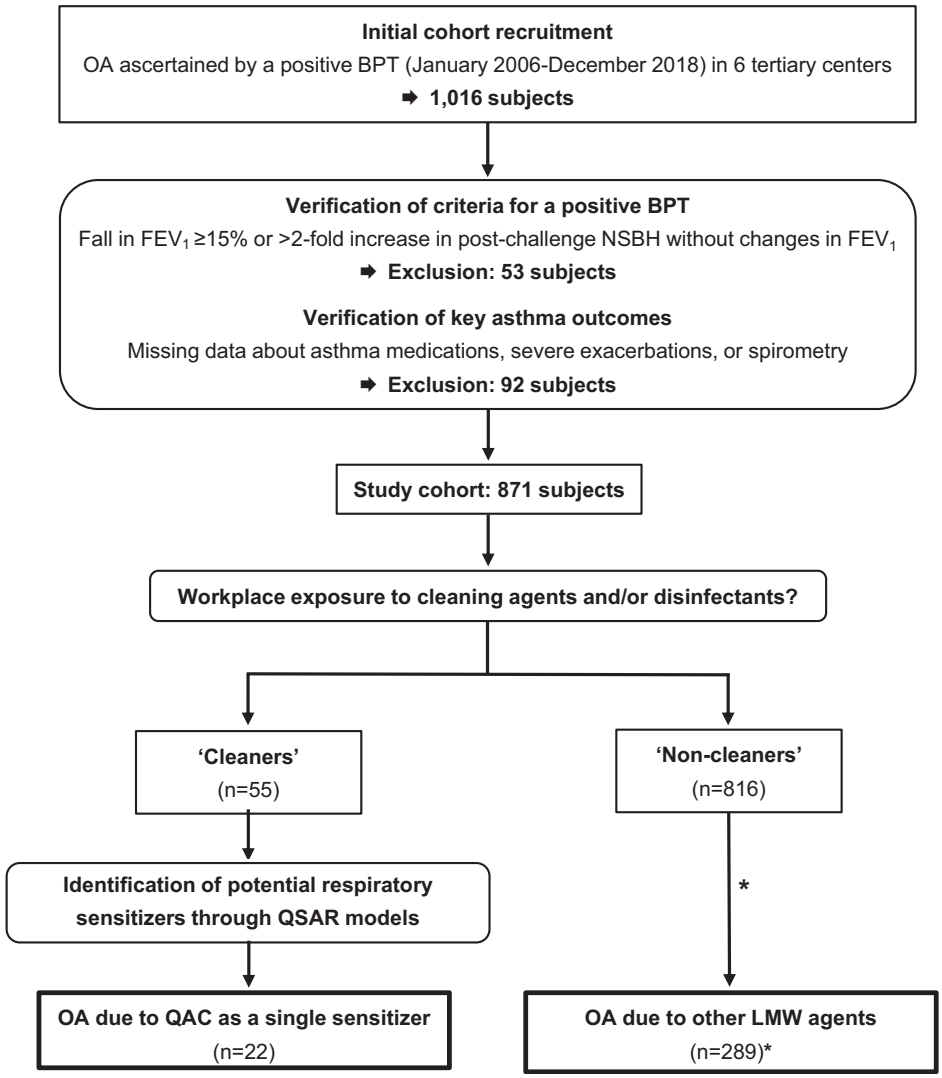

FIGURE 1. Flowchart of the study. Twenty-six subjects with acrylate-induced occupational asthma (OA) were excluded from the initial cohort because this subset was recently documented to demonstrate a distinct phenotype compared with other LMW agents.[19] Nine subjects with OA caused by aldehydes used for noncleaning purposes were also excluded. *BPT*, bronchoprovocation tests; *FEV_1*, forced expiratory volume in 1 second; *LMW*, low molecular weight; *NSBH*, nonspecific bronchial hyperresponsiveness; *QAC*, quaternary ammonium compound; *QSAR*, quantitative structure–activity relationship.

didecyldimethylammonium chloride (n = 16) and benzalkonium chloride (n = 6). No respiratory sensitizer was identified in four subjects with a positive BPT (see Table E4 in this article's Online Repository at www.jaci-inpractice.org for the characteristics of these four subjects). The 22 subjects with QAC-induced OA were compared with 289 subjects with OA caused by various other LMW agents (Table II).

Demographic and clinical characteristics

The E-PHOCAS used a standardized spreadsheet to gather information about (1) causal agents and jobs; (2) demographic and clinical characteristics; (3) timing of work-related respiratory symptoms in relation to exposure to the causal agent; (4) coexisting conditions (ie, physician-based diagnosis of work-related rhinitis, contact urticaria and/or dermatitis, and sinusitis); and (5) materials and methods used for BPT performance.

Lung function assessments

The database collected the baseline forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) values as well as the level of NSBH measured at baseline and 24 hours after challenge exposure. The level of NSBH was categorized as absent, mild, or moderate/severe, according to the bronchoprovocation method used in each center[20,21] (Appendix E2). A significant increase in post-challenge NSBH was defined by a twofold or greater increase in the level of NSBH measured 24 hours after the challenge exposure compared with the baseline value (ie, a baseline/postchallenge ratio of NSBH indices $\geq$2).[25]

Bronchoprovocation tests with occupational agents

Bronchoprovocation tests conformed with international recommendations in terms of safety precautions, placebo challenge, and duration of functional monitoring (Appendix E2).[25] A positive BPT

TABLE I. Potential respiratory sensitizers involved in positive bronchoprovocation tests with cleaning and disinfecting products*

Single sensitizer (n = 30)	n
Quaternary ammonium compounds	
Didecyldimethylammonium chloride (CAS 7173-51-5)	16
Benzalkonium chloride (CAS 8001-54-5)	6
Amines	
Ethanolamine (CAS 141-43-5)	2
Ethylenediamine (CAS 107-15-3)	2
Glutaraldehyde (CAS 111-30-8)	3
Chloramine T (CAS 127-65-1)	1
Multiple potential sensitizers (n = 21)	**n**
Quaternary ammonium compounds†	
Didecyldimethylammonium chloride (CAS 7173-51-5)	12
Benzalkonium chloride (CAS 8001-54-5)	10
Amines	
Ethylenediaminetetraacetic acid (CAS 60-00-4)	4
Lauryldimethylamine oxide (CAS 1643-20-5)	3
N-(3-aminopropyl)-*N*-dodecylpropane-1,3-diamine) (CAS 2372-82-9)	1
Tetraacetylethylenediamine (CAS 10543-57-4)	1
C12-14-alkyltrimethylenediamine (CAS 90640-43-0)	2
N,*N*-Dimethyltetradecylamine *N*-oxide (CAS 3332-27-2)	1
Glutaraldehyde (CAS 111-30-8)	9
Chloramine T (CAS 127-65-1)	7
Chlorhexidine (CAS 55-56-1)	6
Polyhexanide (CAS 28757-47-3)	5
Octenidine dihydrochloride (CAS 70775-75-6)	2
1,2-Benzisothiazol-3(2H)-one (CAS2634-33-5)	2
Sodium dichloroisocyanurate dehydrate (CA# 51580-86-0)	2
Sodium dodecylbenzene sulphonate (CAS 25155-30-0)	3
Enzymes (not detailed)	3
No identified sensitizer (n = 4)	**n**

CAS, Chemical Abstracts Service.
*Potential sensitizers identified using a quantitative structure–activity relationship model.[23]
†Among 21 positive bronchoprovocation tests performed with multiple potential sensitizers, 20 were challenged with products containing quaternary ammonium compounds whereas one subject showed a positive reaction to a cleaning product containing chloramine T and *N*,*N*-dimethyltetradecylamine.

result was defined by either a 15% or greater fall in FEV_1 at any time during the postchallenge monitoring period or a twofold or greater increase in the postchallenge level of NSBH compared with the baseline value.[25]

The BPTs with QACs aimed to recreate as closely as possible the conditions of exposure at the workplace by wiping or brushing (n = 21) and/or spraying (n = 14) the commercial product that contained QAC as the single potential sensitizer (n = 13) or a pure QAC solution (n = 9). The products were diluted in water as recommended by the manufacturer.

Markers of airway inflammation

Data pertaining to markers of airway inflammation included, whenever available, (1) baseline blood eosinophils (assessed within 1 month of the SIC procedure); (2) sputum eosinophils and neutrophils, expressed as a percentage of the total cell count at baseline and 24 hours postchallenge; and (3) fractional exhaled nitric oxide concentration (FeNO) at baseline and 24 hours after the BPT. Detailed information on the methodology used for sputum induction and processing in the participating centers is available in Appendix E2. An eosinophilic response was defined as a postchallenge increase in sputum eosinophil count of 2% or greater (post-BPT minus baseline percentage value). The FeNO level was measured in five of the six centers according to recommendations from both the European Respiratory Society and the American Thoracic Society recommendations.[26]

TABLE II. Low–molecular weight agents involved in occupational asthma in study cohort

Low–molecular weight agent	n
Isocyanates	97
Persulfate salts	53
Metals	26
Wood dusts	25
Welding	22
Metal working fluids	10
Amines	10
Acid anhydrides	9
Epoxy resins	7
Drugs	6
Resins/glues/paints (not otherwise specified)	5
Colophony	5
Reactive dyes	2
Styrene	1
Various low–molecular weight agents	11
Total	289

Data analysis

Quantitative data are presented as a median and interquartile range (IQR). We compared groups of subjects using Fisher exact or χ^2 test for categorical variables and nonparametric tests for numerical variables. A multivariable linear regression analysis was conducted using a generalized linear model and a stepwise procedure based on the Akaike information criterion to select the most parsimonious model among subjects with an available sputum assessment and a positive BPT to QACs or other LMW agents (n = 79), to explore factors that determined the magnitude of post-BPT change in sputum eosinophils (ie, the difference between the post- and pre-BPT sputum eosinophil count expressed as a percentage of total nonsquamous cells). Potential confounding factors (ie, independent variables) incorporated into this regression included a positive BPT induced by QACs (yes or no), age, sex, smoking status (current and exsmokers versus never-smokers), treatment with inhaled corticosteroid at the time of the BPT (yes or no), baseline sputum eosinophil count (percent total nonsquamous cells), and time elapsed since last work exposure (≤1 month vs >1 month). We performed statistical analysis using R software (version 3.4.1; R Foundation, Vienna, Austria). *P* less than .05 was considered significant.

RESULTS

Clinical and occupational characteristics

A total of 22 subjects with a positive BPT to QACs as the single identified sensitizer, including benzalkonium chloride (n = 6) and didecyldimethylammonium chloride (n = 16) were identified. These subjects most commonly worked in health care environments (n = 14) and were cleaners (n = 6), nurses (n = 5), one hospital

TABLE III. Clinical and functional characteristics of subjects with occupational asthma caused by QACs compared with other low−molecular weight agents*

Characteristic	Occupational asthma owing to QACs (n = 22)	Occupational asthma owing to other low−molecular weight agents (n = 289)	*P*
Age, y (median [IQR])	45 (40-52)	44 (34-52)	.295
Sex (female)	19 (86.4)	115 (39.8)	**<.001**
Body mass index, kg/m^2 (median [IQR])	28.6 (22.8-33.03)	26.7 (24-29.8)	.536
Smoking habit			**.016**
Current/ex-smoker	6 (27.2)	157 (54.3)	
Never-smoker	16 (72.7)	132 (45.7)	
Atopy†	11 (50.0)	117 (42.1)	.507
Asthma preexisting to causal exposure	3 (13.6)	28 (9.7)	.470
Duration of exposure before asthma onset, mo (median [IQR])	75 (12-150)	82 (30-193)	.245
Duration of symptomatic exposure, mo (median [IQR])	28 (8-54)	29 (12-38)	.621
Interval since last work exposure, mo (median [IQR])	0.6 (0.1-6)	1.7 (0.1-10.0)	.775
Coexisting condition			
Work-related rhinitis	10 (45.5)	167 (58.0)	.271
Chronic rhinosinusitis	4 (18.2)	37 (12.8)	.510
Work-related urticaria	2 (9.1)	24 (8.4)	.706
Work-related contact dermatitis	5 (22.7)	37 (12.9)	.198
Asthma treatment/severity at work‡			
No treatment	3 (13.6)	48 (16.6)	.283
Mild (GINA treatment steps 1-2)	7 (31.8)	44 (15.2)	
Moderate (GINA treatment step 3)	6 (27.3)	87 (30.1)	
Severe (GINA treatment steps 4-5)	6 (27.3)	110 (38.1)	
Inhaled short-acting β_2-agonist ≥1/d	6 (27.2)	97 (33.6)	.643
≥1 severe asthma exacerbation (past 12 mo)	7 (31.8)	79 (27.3)	.628
Baseline spirometry			
FVC, % predicted (median [IQR])	108 (100-114)	96 (86-107)	**.002**
FEV_1, % predicted (median [IQR])	96 (89-110)	89 (80-98)	**.029**
FEV_1 <80%	4 (18.2)	72 (24.9)	.611
FEV_1/FVC (median [IQR])	78 (73-82)	76 (70-81)	.390
FEV_1/FVC <70%	4 (18.2)	70 (24.2)	.614
Maximum fall in FEV_1 (% from baseline value)	22 (18-27)§	23 (18-29)§	.441
Baseline level of NSBH	(n = 22)	(n = 272)	.916
Absent	5 (22.7)	76 (27.9)	
Mild	12 (54.5)	138 (50.7)	
Moderate to severe	5 (22.7)	58 (21.3)	
Postchallenge change in NSBH	(n = 11)	(n = 177)	
Pre/postchallenge NSBH ratio (median [IQR])	3.0 (1.5-4.1)	2.0 (1.0-4.0)	.289
Pre/postchallenge NSBH ratio ≥2	8 (72.7)	88 (49.7)	.214
Pattern of bronchial response to bronchoprovocation tests	(n = 20)§	(n = 255)§	.729
Isolated early reaction	7 (31.8)	61 (21.7)	
Isolated late reaction	7 (31.8)	99 (35.2)	
Dual reaction	6 (27.3)	95 (33.8)	

FEV$_1$, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *IQR*, interquartile range; *NSBH*, nonspecific bronchial hyperresponsiveness; *QAC*, quaternary ammonium compound.

*Data are presented as n (% available data) unless otherwise specified. Values in bold are statistically significant.

†Atopy was defined by the presence of at least one positive skin prick test result to common allergens.

‡The severity of asthma was graded according to treatment steps proposed by the Global Initiative for Asthma (GINA)[27] as untreated (step 0), mild (steps 1-2), moderate (step 3), or severe (steps 4-5).

§The BPT was considered positive based on a significant increase in the postchallenge level of NSBH compared with the baseline value (ie, pre/postchallenge NSBH ratio of ≥2) in the absence of a ≥15% fall in FEV_1 in two of the 22 subjects challenged with QACs and in 34 of the 289 subjects challenged with other low−molecular weight agents.

technologist, one dental assistant, and one administrative worker, or were in food processing facilities (n = 4). Another two subjects were domestic cleaners, and two subjects were employed in educational services. Notably, two of these subjects were administrative employees with indirect exposure to cleaning products in a health care facility and a school.

Table III lists clinical and functional characteristics of subjects with OA caused by QACs. Compared with OA caused by other

TABLE IV. Airway inflammation markers in subjects with OA caused by quaternary ammonium compounds compared with other low−molecular-weight agents*

Characteristic	OA owing to quaternary ammonium compounds (n = 22)	OA owing to other low−molecular-weight agents (n = 289)	*P*
Blood eosinophils	(n = 13)	(n = 150)	
Cells/μL (median [IQR])	244 (190-460)	229 (159-400)	.451
>300/μL	6 (46.2)	56 (37.3)	.561
Baseline FeNO	(n = 15)	(n = 98)	
ppb (median [IQR])	23 (13-38)	19 (10-31)	.528
Postchallenge FeNO			
ppb (median [IQR])	25 (15-50)	26 (15-52)	.912
Change (ppb) (median [IQR])	4 (−1 to 7)	6 (1-18)	.324
Baseline sputum eosinophils	(n = 8)	(n = 71)	
% (median [IQR])	6.0 (2.0-10.0)	1.0 (0.6-5.0)	**.052**
≥3%	5 (62.5)	26 (36.6)	.252
Postchallenge sputum eosinophils			
% (median [IQR])	24.2 (17.6-29.2)	4.0 (2.0-9.0)	**<.001**
Change compared to baseline value (%)(median [IQR])	18.1 (12.1-21.1)	2.0 (0-5.2)	**<.001**
Increase ≥2%	8 (100)	37 (52.9)	**.009**
Baseline sputum neutrophils	(n = 8)	(n = 71)	
% (median [IQR])	46.5 (36.4-60.1)	55 (40-68)	.597
Postchallenge sputum neutrophils			
% (median [IQR])	51.8 (46.7-60.8)	56 (35-68)	.715
Change compared with baseline value (%)(median [IQR])	3.0 (−7.4 to 6.4)	1.0 (−12.1 to 14.4)	.726

FeNO, fractional exhaled nitric oxide; *IQR*, interquartile range; *OA*, occupational asthma
*Data are presented as n (% available data) unless otherwise specified. Values in bold are statistically significant ($P < .05$).

TABLE V. Multivariate regression analysis for changes in postchallenge sputum eosinophil count*

Independent variable	Adjusted β coefficient (95% confidence interval)		*P*
Challenge with quaternary ammonium compound as single-sensitizer (yes/no)	10.778	(3.625 to 17.932)	**.004**
Age, y	0.069	(−0.114 to 0.252)	.457
Female sex	2.663	(−2.015 to 7.340)	.260
Current and ex-smoker vs never-smoker	−3.185	(−7.367 to 0.996)	.133
Treatment with inhaled corticosteroid at time of bronchoprovocation test (yes/no)	2.146	(−2.226 to 6.517)	.331
Baseline sputum eosinophil count (%)	−0.054	(−0.379 to 0.271)	.742
Time elapsed since past work exposure (≤1 mo vs >1 mo)	0.506	(−3.519 to 4.530)	.803

*This multivariate linear regression model incorporated 79 subjects with available sputum analysis and a positive bronchoprovocation test to quaternary ammonium compound or other low−molecular weight agents. Bold indicates statistical significance ($P < .05$).

LMW agents, QAC-induced OA was associated with a significantly higher proportion of women and never-smokers. Subjects with QAC-induced OA had greater median FVC and FEV_1 values, whereas the FEV_1/FVC ratio did not differ between groups. There was no difference in the level of baseline NSBH or the pattern of asthmatic reactions during the BPT between subjects with OA caused by QACs and those challenged with other LMW agents. Among subjects with QAC-induced OA, a twofold or greater increase in the postchallenge level of NSBH was recorded in eight of 11 subjects with an available postchallenge measurement of NSBH (72.7%), a proportion that tended to be higher, but not significantly so, than that of OA caused by other LMW agents (88 of 177; 49.7%).

Markers of airway inflammation

Suitable pre- and postchallenge sputum samples were available in only eight of 22 subjects with QAC-induced OA (36.4%) and in 71 of 289 with a positive BPT to other LMW agents (24.6%; $P = .220$) (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). The median (IQR) baseline sputum eosinophil count was slightly higher (6.0% [2.0% to 10.0%]) in the eight subjects with QAC-induced OA than in those with OA caused by other LMW agents (1.0% [0.6% to 5.0%]; $P = .052$) (Table IV). Positive BPTs with QACs were associated with a significantly greater median (IQR) postchallenge increase in sputum eosinophils (18.1% [12.1% to 21.1%]) compared with the other LMW agents (2.0% [0% to 5.2%]; $P < .001$). An eosinophilic response (ie, ≥2% postchallenge increase in sputum eosinophils) was significantly more frequent (all eight subjects) in QAC-induced OA than in subjects with a positive BPT elicited by other LMW agents (37 of 71 subjects [52.1%]; $P = .009$). Multivariate regression analysis retained only a positive BPT induced by QACs as a factor associated with a greater increase in post-SIC sputum eosinophils (Table V). There were no differences between OA caused by QACs and the other LMW agents with regard to baseline blood eosinophil counts as well as baseline and postchallenge FeNO values.

DISCUSSION

As far as we know, this study is the first attempt to characterize the clinical, functional, and inflammatory pattern of QAC-induced OA. The findings indicate that challenge exposure to QAC is associated with an increase in NSBH and a highly eosinophilic airway response, features that are consistent with an immunologically mediated sensitizing mechanism.

Although a number of reports documented asthmatic reactions after challenge exposure to QACs,[3-7] the inflammatory pattern induced by these chemicals has not been specifically investigated. Previous studies reported an increase in sputum eosinophils after challenge exposure to the causal agent in subjects with OA independently of the type of agent (ie, LMW vs high−molecular weight agents) and the pattern of asthmatic reaction (ie, late vs early reactions).[20,28] Nevertheless, a previous analysis of the E-PHOCAS cohort demonstrated that BPTs with acrylate compounds were more frequently associated with a significant increase in sputum eosinophils (88%) compared with other LMW agents (48%).[19] On the other hand, acrylate-induced OA was more frequently associated with work-related rhinitis, and acrylate compounds elicited a significantly higher increase in postchallenge FeNO compared with other LMW agents, whereas QACs failed to induce such changes in FeNO. Taken together, these observations highlight the heterogeneous nature of OA caused by LMW agents and the need to explore differences in underlying pathobiologic pathways. It was recently demonstrated in a murine model that dermal exposure to the QAC dodecyl dimethylammonium bromide can induce the activation of type 2 innate lymphoid cells (ILC2s) in the skin.[29] Murine models of allergic asthma showed that ILC2s are a potent source of the T_H2 cytokines IL-5 and IL-13 and are able to induce eosinophil recruitment, mucus hypersecretion, and NSBH,[30] although the role of ILC2s in the development of airway sensitization to LMW chemicals warrants further investigation. Alternative mechanisms including neurogenic inflammation and mast cell degranulation resulting from direct stimulation of chemoreceptors at nerve endings, especially the transient receptor potential channels, remain purely speculative in the case of QACs.[31]

The immunologic mechanisms involved in the inception of OA caused by QACs remain largely unknown. Several reports of urticaria caused by QACs may support the possibility of an immediate-type, IgE-mediated, allergic mechanism.[32] However, in previous reports of subjects with QAC-induced OA, skin-prick tests with QACs elicited an immediate skin response in only one subject with associated urticaria, whereas these tests were not completed in other subjects.[3,5,7] Specific IgE antibodies against quaternary ammonium were not detected[4,5] or their presence did not correlate with asthma symptoms.[16] We did not conduct skin-prick tests or a determination of a specific IgE in subjects included in the current cohort. It is currently acknowledged that LMW agents causing asthma are incomplete antigens (ie, haptens) that combine with amino acid residues on airway proteins to become immunogenic.[33,34] However, the potential diversity of chemical interactions with airway proteins could explain heterogeneous pathobiologic responses and our inability to identify specific IgE in OA caused by most LMW agents.

Most subjects with QAC-induced OA (63.6%) in our series were exposed to QACs in health care environments. Exposure to cleaning and disinfecting products in health care settings has been associated with an increased risk for new-onset asthma in nurses and related occupations,[10,11] with current asthma in hospital cleaners,[12] and with work-related asthma symptoms in health care professionals.[13] These studies revealed broad categories of tasks or products associated with asthma, such as general-purpose cleaning and instrument cleaning/sterilization,[11,13,35] but they failed to identify specific agents involved in asthma onset. Using a specific job−task−exposure matrix, the Nurses' Health Study II[15] found that poor asthma control was associated with exposure to aldehydes, hypochlorite bleach, hydrogen peroxide, and enzymatic cleaners, but not with QACs. Our data provide clinical evidence supporting the findings of Gonzalez et al,[16] who established a significant relationship between exposure to QACs and an increased likelihood of physician-diagnosed asthma at work among hospital health care workers.

Strengths and limitations

The strength of this study was its multicenter design, which allowed a large series of patients with QAC-induced OA confirmed by BPT to be gathered after the exclusion of subjects concomitantly challenged with other potential respiratory sensitizers contained in cleaning products. Nevertheless, several limitations deserve further careful consideration. The major limitation of this study results from the limited number of subjects with available sputum samples. Nevertheless, the multivariate regression analysis confirmed that challenge exposure to QACs was the most significant determinant of the magnitude of the eosinophilic response to BPT in this cohort of subjects with OA induced by LMW agents, independently of potential confounders. In addition, the comparison of subjects with and without sputum samples suggests that there was no bias toward the performance of induced sputum in subjects with a higher likelihood of eosinophil recruitment in the airways. Indeed, Prince et al[28] found that a lower baseline sputum eosinophil count, nonsmoking status, and shorter exposure to the causal occupational agent were the only independent predictors for a greater eosinophilic response after BPTs with occupational agents.

This study may also be criticized on the grounds of its retrospective design and the use of different (although validated) methods for assessing NSBH and sputum cells. However, these between-center differences in procedures are unlikely to have affected the findings because the collection and interpretation of data were standardized for the whole cohort. Although, the reference method for establishing a diagnosis of OA,[36,37] BPT, is not thoroughly standardized, the centers participating in this cohort conformed to the main methodologic requirements for safety and reliability issued by the European Respiratory Society, and airway responses to challenges exposures were interpreted using uniform criteria.[25]

Another limitation arises from the lack of quantitative assessment of exposure to QACs at the workplace and during BPTs. Dose-dependent bronchoconstriction induced by nebulized benzalkonium chloride (formerly used as a preservative in nebulizer solutions) has been described in asthmatic patients, although changes in NSBH and airway eosinophils have not been documented in such human inhalation studies with benzalkonium chloride.[17,18,38] On the other hand, there is currently little information about exposure−response relationships because QACs have a low vapor pressure, and accurate sampling and

analytical methods have only recently been developed to detect very low levels of QACs in the air.[39]

The potential role of irritants was not systematically investigated in this study because evidence-based and validated lists of substances that should be considered as respiratory irritants are currently lacking.[40] Epidemiologic studies,[9,10,12,13] surveillance programs,[23,41] and case series[42] have most commonly related asthma in cleaners to respiratory irritants such as bleach, ammonia, acids, and oxidizers, although OA and work-exacerbated asthma could not be differentiated in those studies and specific causal agents were not identified because BPTs were generally not performed. The cleaning and/or disinfectant products that induced a positive BPT in 22 subjects with QAC-induced OA in this cohort did not contain known respiratory irritants. However, four subjects in the cohort developed an asthmatic response during BPT with cleaning or disinfecting chemicals (ie, peracetic acid in three subjects and sodium octyl sulfate in one) that failed to meet structural requirements for being considered respiratory sensitizers[23] (Table E4). These findings further support previous reports of asthmatic reactions induced by peracetic—acetic acid mixtures[43,44] and the possible role of irritant ingredients in the development of cleaners' asthma. Interestingly, the positive BPT responses in the subjects of the current study were not associated with an increased level of NSBH or sputum eosinophils, which is consistent with the findings of Sastre et al,[45] who performed inhalation challenges with bleach in 13 cleaners.

CONCLUSION

Despite its inherent limitations, this retrospective study provides further insight into the inflammatory mechanisms involved in the development of QAC-induced OA by demonstrating that the condition is associated with a highly eosinophilic airway response. The findings also highlight the respiratory sensitizing potential of these widely used biocide compounds. Awareness of this possibility may be relevant to the investigation of work-related asthma symptoms in workers involved in cleaning and disinfection tasks. Further prospective investigation of inflammatory markers and immunologic mechanisms involved in QAC-induced OA is required to confirm and expand the findings of our retrospective study.

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