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An Official American Thoracic Society Proceedings: Work-related Asthma and Airway Diseases.

Presentations and Discussion from the Fourth Jack Pepys Workshop on Asthma in the Workplace

Susan M. Tarlo and Jean-Luc Malo, on behalf of the Fourth Jack Pepys Workshop on Asthma in the Workplace Participants

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Abstract

Work-related asthma is a common occupational lung disease. The scope of the Fourth Jack Pepys Workshop that was held in May 2010 went beyond asthma to include discussion of other occupational airway diseases, in particular occupationally related chronic obstructive pulmonary disease (COPD) and bronchiolitis. Aspects explored included public health considerations, environmental aspects, outcome after diagnosis, prevention and surveillance, and other work-related obstructive airway diseases. Consistent methods are needed to accurately estimate the comparative burden of occupation-related airway diseases among different countries. Challenges to accomplishing this include variability in health care delivery, compensation systems, cultural contexts, and social structures. These factors can affect disease estimates, while heterogeneity in occupations and workplace exposures can affect the underlying true prevalence of morbidity. Consideration of the working environment included discussion of practical methods of limiting exposure to respiratory sensitizers, methods to predict new sensitizers before introduction into workplaces, the role of legislated exposure limits, and models to estimate relative validity of various ameliorative measures when complete avoidance of the sensitizer is not feasible. Other strategies discussed included medical surveillance measures and education, especially for young individuals with asthma and new workers about to enter the workforce. Medical outcomes after development of sensitizer-induced occupational asthma are best following earlier diagnosis and removal from further exposure, but a subset may be able to continue working safely provided that exposure is reduced under close follow-up monitoring. It was recognized that occupationally related COPD is common but underappreciated, deserving further study and prevention efforts.

Keywords: work-related asthma; occupational asthma; work-exacerbated asthma; occupational COPD

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Executive Summary

Several areas of importance in work-related asthma were reviewed and discussed. Main conclusions reached were:

- There has been increased understanding of the relative risk of work-related asthma (WRA) and the public health impact in developed nations, but comparisons between countries remain difficult to interpret. Better comparisons could be made if there is standardization of methods used to assess frequency and relative causes of occupational asthma (OA).
- Better preventive measures are possible but may require government legislation to prevent the introduction of new sensitizing agents and to implement early detection of sensitization and disease.
- There is a need for more research to understand the socioeconomic and medical risks and benefits that may result from a reduction in exposure rather than complete elimination of exposure for subsets of patients with sensitizer-induced OA.
- Work-exacerbated asthma (WEA) and other work-related airway diseases have emerged as important but are often diagnoses of exclusion, and many are likely under-recognized due to the lack of specific diagnostic criteria or lack of epidemiologic studies showing new causes of airway diseases. Ongoing efforts should be made to identify such diseases and develop diagnostic criteria.

Introduction

The Fourth Jack Pepys Workshop, held in Toronto in May 2010, emphasized public health and preventive aspects of work-related asthma, with consideration of other airway diseases (bronchiolitis obliterans, chronic obstructive pulmonary disease). Methods are provided in the online supplement. There were five themes: these proceedings summarize the workshop and discussion.

Theme 1: Public Health Considerations

Presentation: M. S. Jaakkola

Discussion leaders: J. Beach, J. L. Malo, and M. F. Jeebhay

Discussion contributors: M. Becklake, N. Cherry, G. Delclos, J. Turcot, R. Copes, F. Labrèche, M. Ribeiro, and A. Curran

Work-related asthma (WRA) includes both occupational asthma (OA) and work-exacerbated asthma (WEA). The former describes asthma that is caused by work, while the latter describes asthma that is exacerbated by work. While WRA is a well-recognized impediment to work, asthma that is not work-related can also impair an individual's inability to work (1). Accurate estimates of occurrence are essential when establishing public health policies.

The state-of-the-art review for this section was based on an article subsequently published (2). Emphasis was placed on the need to define both the numerator and denominator when estimating OA occurrence based on identified cases. A summary of the advantages and limitations of the various methods is given in Table 4 of that publication (2).

Discussion

Variable estimates of occurrence. The variability of the estimates of occurrence can be illustrated by two studies. The European Community Respiratory Health Study (ECRHS) study (3) reported a risk of new-onset asthma of 250 to 300 cases per million per year. In contrast, the Surveillance of Work-related Occupational Respiratory Disease (SWORD) 2005 publication from the United Kingdom reported only 22 cases per million per year (*see below*). Per-industry asthma risks have also been shown to vary in developing countries (4), such as China (5), Nigeria (6), and Pakistan (7).

The variable estimates may be due, in part, to differences in the ability or willingness of individuals to pursue the diagnosis of WRA and subsequently leave workplaces if necessary (i.e., populations in which individuals are less likely to seek a diagnosis and leave the workplace provide larger estimates of the prevalence of WRA). Among the factors that contribute to delays in diagnosis or changing job are older age, low education, fear of losing a job, lack of workplace safety committees (8, 9, 10), and perhaps expectations of symptoms. For example, among cleaners or woodworkers, there may be an expectation of irritant symptoms that leads workers to delay reporting their symptoms. Among the factors that contribute to delays in leaving the workplace are older age and higher income (9).

Sex-related differences may also contribute to the variability of the estimates, since sex affects both the occurrence of WRA and the reporting of symptoms (11). With respect to occurrence, women in some professions have a greater risk of OA than do men. As examples, women snow crab workers (12) and women fish-processing workers in South Africa (13) have a greater risk of developing OA that is independent of exposure. With respect to reporting symptoms, differential reporting by women and men may affect the recognition of WRA. As examples, men mainly report cough and sputum, while women primarily report shortness of breath (11).

Since female sex is associated with increased disease risk, and education level is inversely associated with workplace exposures and WRA, analyses that adjust for sex and education may underestimate the risk of WRA. Options to avoid this include assessing interactions, leaving certain variables out of the equation, or stratifying.

Effects of pre-existing asthma. Pre-existing asthma is a major risk factor for work-exacerbated asthma and increases risk of sensitization to occupational agents. It may be expected that young adults with asthma in adolescence would avoid jobs with exposure to respiratory irritants, but this was not confirmed (14, 15). Young individuals with asthma seldom consider their asthma in career plans (16) although those with more symptomatic asthma in childhood are less likely to be exposed at work to dusts, fumes, or gases (17).

Using databases to estimate occurrence. Large population databases do not generally record industry or occupation and, therefore, often are not suitable for estimating the occurrence of WRA. An approach from the province of Alberta, Canada linked a database of all submitted workers' compensation claims (asthma and nonasthma), where occupation was documented, with a health care billing database that included asthma (18) and estimated the relative incidence of new-onset asthma among different occupations. Under-reporting of OA was found (i.e., a ratio of 1:1.83 to 1: 24.4 was proposed, compared with rates extrapolated from SWORD [19] and Finland [20], respectively). Other population studies have shown increased odds ratios for asthma in occupations/exposures that are not well recognized as causes of asthma, including entertainers (21), postal and communication workers (in Chinese women [5]), and individuals who work with paper dust and carbonless copy paper (in Finland [22]).

Other. Additional items included in the discussion included all of the following:

- The role of nonspecific irritants for WRA. Cold air and exercise are known to exacerbate asthma but are more recently recognized in endurance sports to be associated with epithelial damage and airway hyperresponsiveness (23, 24).
- A suggestion that to clarify the differences between population-based and clinical case-based estimates of prevalence, population studies should assess a representative sub-sample to determine the proportion of cases with a valid diagnosis of OA or WEA.
- The disconnect between WRA guidelines and practitioner practice (25). As an example, in Catalonia, only about 8% of primary care physicians even recorded an occupational history (26).
- The observation that symptoms of WEA are common in clinical settings but episodes are difficult to document because they may be transient.

Theme 2: Environmental Considerations

Presentation: D. Heederik

Discussion leaders: G. Liss and P. Henneberger

Discussion contributors: D. Bernstein, D. Heederik, T. Sigsgaard, J. L. Malo, D. Fishwick, G. Moscato, J. Beach, P. Harber, P. S. Burge, A. Siracusa, X. Baur, S. Tarlo, I. Kudla, and B. Nemery

OA can be caused by sensitizers of high molecular weight (usually proteins) or of low molecular weight (chemicals). Alternatively, OA can be irritant-induced (e.g., reactive airways dysfunction syndrome [RADS]). The REACH system requires evaluation of new chemicals entering the market in regards to their toxic and sensitizing potential. Results from this system are being implemented in North America and Asia. However, REACH generally does not include substances used in production processes (enzymes), food products (cereal grains), and other natural materials (wood).

Even simplistic techniques providing average exposures over a work shift consistently show exposure–response relationships indicating lower risk for OA and work-related sensitization at lower exposure levels. Thus exposure reduction is expected to lead to lower disease incidence. However, the relevance of peak exposures (height or frequency of peaks or a combination) is unclear.

Job exposure matrices do not accurately capture potential heterogeneity between jobs and industries. For diisocyanates, the risk of specific sensitization relates to the level of exposure; dermal symptoms were suggested as a proxy of exposure.

Modeling studies can help to address the effect of reducing exposure on the burden of disease for a particular population (27, 28). In the Netherlands, a 1% excess risk has been considered acceptable for occupational allergens for use as the critical value in risk assessment (29).

Elimination of the use of occupational sensitizers is the ideal primary preventive measure. There is strong evidence that exposure elimination of latex (mainly powdered gloves) is associated with reduction in OA. In contrast, bakery and spray painting environments are technically and hygienically much more complex. Pragmatic multi-component interventions to diminish exposures are often not executed at the same time, in the same way, or separately from other preventive measures; each industry is different, making effects of individual interventions extremely difficult to evaluate.

Finally, exposure reduction models (as used in public health for obesity, smoking, etc.) should also be considered to simulate results from certain exposure reduction measures or complex interventions as has been reported in bakeries (27).

Discussion

Besides animal models, another means of predicting the potential for sensitization for new chemicals that are introduced in workplaces is a computerized quantitative structure-activity program that is freely available and offers a prediction of risk of sensitization according to the molecular structure (30).

Material Safety Data Sheets are often insufficient and inaccurate. In a recent survey of diisocyanate-containing products performed in Canada, a high proportion of sheets did not mention asthma, which is surprising in the case of a well-known sensitizer. Few validated occupational allergens are available for immunological testing, and their commercial development is not profitable. The same efforts that have been made in providing satisfactory extracts for skin sensitizers should be made for respiratory sensitizers.

Workers can be exposed to several sensitizers at the same time. However, in bakeries the focus has only been to reduce exposure to one or two major allergens. Avoiding powdered forms of sensitizers, and instead using granules or liquids, can reduce exposure and risk (e.g., psyllium, detergent enzymes, and persulfates). For other exposures, the causal allergens are unknown and the only approach is a basic combination of hygiene practices.

Multiple exposures to irritants and sensitizers can increase the risk both of OA and work-exacerbated asthma, but direction of interactions can differ; for example, endotoxins have a protective effect on sensitization (31) but also cause airway inflammation (32). Generally, inhaled irritants increase the risk of respiratory symptoms whereas exposure to sensitizers also increases the risk of hyperresponsiveness (33). Occupational allergens can be brought home, and there can even be an effect of increasing risk of atopic diseases among children from their mother's work during pregnancy (34).

In The Netherlands, if a baker is referred for OA, exposure assessment is included. Hygienists visit the workplace and are part of the medical team. Although costly, at least one Canadian center also anecdotally indicates benefit from a multidisciplinary approach that includes physicians, a hygienist, a nurse, and a return-to-work coordinator.

There is room for improved safety training of workers. Among cleaners, poor understanding of safety training was associated with respiratory symptoms (35). Workers with asthma often do not take asthma into consideration when they go to work where there are fumes and dusts (16). Few high school programs provide education on recognizing and preventing WRA.

Mechanisms by which exposure to irritants increases the risk of sensitization and OA should be examined. The role of skin absorption in sensitization is an important question. Applying persulfate salts on the skin and then challenging animals by the airway results in increased reactivity to methacholine and immunological alterations on the following day (36).

Theme 3: Outcome after Diagnosis of Sensitizer-Induced OA

Presentation: R. Merget

Discussion leaders: O. Vandenplas, P. Harber, and A. Cartier

Discussion contributors: Y. Cloutier, M. Labreque, K. Lavoie, C. Lemière, K. Pacheco, X. Munoz, S. Quirce, S. Burge, P. Cullinan, D. Fishwick, P. Maestrelli, C. Mapp, L. Perfetti, S. Brooks, and G. de Groene

Should Exposure to the Causal Agent Be Completely or Partially Stopped?

The usual exposure recommendation for optimum medical management of OA caused by a sensitizer has been to completely avoid further exposure to that agent. The additional question of reduction versus elimination of exposure was raised.

A previous Agency for Healthcare Quality and Research (AHRQ) systematic

review that included management of OA found insufficient comparable studies to perform formal grouped analyses for outcomes after changes in work exposures (37). There were few data on reduction of exposure, and conclusions could not be drawn.

A later systematic review (38) of outcome after stopping exposure for an average of 31 months reported recovery rates of 0 to 100% with a pooled estimate of 32% (95% confidence interval [CI], 26–38%). The pooled prevalence of persisting airway hyperresponsiveness was 73% (95% CI, 66–79%). Worse outcomes were reported from clinic populations, older subjects, longer total duration of exposure and duration of exposure with symptoms, and high-molecular-weight versus low-molecular-weight agents. However, the data were not sufficiently consistent to make sound conclusions on associated factors.

A better prognosis was found in workers with better lung function and milder airway hyperresponsiveness at the time of diagnosis of OA (39, 40). Five studies assessed outcome related to the duration of exposure with OA from various sensitizers (41–46), all showing a shorter duration of exposure after the onset of symptoms in those who had clearing of symptoms at follow-up. The duration of follow-up can affect results as further improvements may be found 2 years or more after stopping exposure (47). Other potential factors for which there is insufficient evidence include smoking, medication, duration of exposure at work before the onset of asthma, specific agent, high- versus low-molecular-weight agent, type and severity of response to specific challenge, age, sex, and atopy.

Seven studies compared outcome of OA in those (not randomized) who left exposure versus those reducing exposure. Four studies found a better outcome in those who stopped exposure (42, 43, 45, 48) and three studies showed a similar outcome in those who reduced exposure (49–51). Pooled analyses (51), and an evidence-based review (52), similarly concluded that asthma outcome was better with complete removal. However, two studies in bakers, not included in the previous analyses (53, 54), reported good symptomatic control by reduced exposure in addition to medical management. Overall, despite a relative paucity of studies there is enough information to conclude that a better outcome of OA occurs with removal than reduction of exposure.

Discussion. Conclusions from a Cochrane review (55) confirmed benefit from stopping versus continuing exposure but, as with the earlier AHQR review (37), considered the data too limited to draw conclusions on reducing exposure.

Practical aspects that affect the decision to stop or reduce exposure were discussed. The negative socioeconomic effects of leaving work and difficulties in finding a job without exposure were emphasized and may represent a trade-off versus benefits on asthma from leaving work. There likely are some patients who can work with reduced exposure without significant worsening of their asthma: the phenotypes of such patients need to be examined. If patients elect to continue working in areas with lower exposures, they require careful monitoring at regular intervals and appropriate interventions.

Other factors that may predict outcome were discussed. Patients who underwent specific challenges for diagnosis and showed increased sputum eosinophils after challenge appeared to have a better asthma outcome 4 years after leaving exposure (56). Those with noneosinophilic inflammatory changes in sputum appear to have a lower FEV_1 and greater decline in FEV_1 over time (56).

An additional consideration is potential bias from the source of the populations in published studies of outcomes. An example (unpublished) was presented by K. Pacheco of laboratory animal workers who were asked whether they had allergic or asthma-like symptoms with animals at work. Thirty-three percent of 167 workers reported symptoms but only 11% had stopped working with the animal in question. Of 108 with a positive allergy skin test to a laboratory animal, only 8% avoided that animal. Questions are raised as to the natural history of such symptoms and sensitization and also why some workers decline or defer medical investigation of symptoms. A study in laboratory animal workers followed for 10 years from the time of apprenticeship (57) showed that among 55 with a positive skin test during apprenticeship, 16 had improvement in the size of the skin test response at follow-up, including 11 who had an initial wheal diameter of 3 mm or greater that was 0 mm at follow-up. Among published studies that reported outcome with reduction in exposure, details of the extent of reduction or measured levels are generally not provided. Some workers sensitized to diisocyanates can have a positive specific challenge even after many years of avoiding exposure, while apparent tolerance may develop in others.

Compensation Issues

Evaluation of impairment from airway disease (asthma or COPD) differs in various compensation systems. In Germany, a percentage impairment rating was developed based on symptoms including frequency of exacerbations, physical examination, spirometry, body plethysmography, exercise testing, and medication requirements—more extensive parameters than recommended in the current ATS guidelines (58). Discussion raised the issue that the practical implications of physiologic losses need to be considered for disability and compensation. The effects on life and work may depend on any accommodation that the employer is able to make for the job (changes in ventilation, work area) and in some cases use of respirators. Often there is little known by the assessing physician about the specific workplace exposure.

Discussion. Occupational rhinitis can contribute to disability. Although allergic rhinitis from sensitizers may often resolve after leaving exposure, there can be persisting significant symptoms from rhinitis resulting from irritant exposures. Significant absenteeism, "presenteeism," and impaired measures of quality of life have been related to rhinitis symptoms, suggesting that these also should be considered in impairment ratings. Comorbidities such as anxiety or depression may also affect ability to work and compliance with medication use and should be considered in the assessment of disability and compensation.

Costs of OA include direct costs (medical care, income loss, costs for a family caregiver), society costs (loss of productivity, replacement worker costs) and future health costs (from the compensation system and general health care costs). In the United Kingdom, the employer pays only a minimal proportion (about 3%) of the lifetime costs, with the remainder equally split between the individual and government, so the employer may have little incentive to prevent disease and impairment.

The right of a worker to continue to work despite OA was questioned. In the United States, this is covered by the Americans with Disability Act. Those making the decisions with workers need to know the local legislation as to the right of an employer to terminate employment of a worker with OA and who should be responsible if they stay and worsen.

Theme 4: Prevention and Surveillance

Presentation: P. Cullinan

Discussion leaders: S. Tarlo, J. Walusiak, P. S. Burge, and C. Redlich

Discussion contributors: M. Labrecque, M. F. Jeebhay, G. Moscato, and A. Siracusa

OA exists in very different environments, which makes the approaches to prevention complex. Bakers may work in large plants with highly controlled exposures or in small craft bakeries employing a few people with relatively heavy exposures. OA is also a fragmented disease because most employers are going to see only one or two cases. Finally, jurisdictions related to prevention differ greatly from one country to the next.

A multidisciplinary team approach including epidemiologists and hygienists may be most effective (25). Identification of work-related allergy, particularly WRA, in the Dutch (nationwide) medical surveillance program among bakery workers is based on an efficient strategy that makes use of diagnostic rules. Bakers at high risk of having work-related allergy are identified by a questionnaire-based prediction model. Sequential diagnostic investigations are performed only in those with an elevated risk.

National and regional surveillance schemes potentially provide one method of assessing temporal trends and the success or otherwise of preventive activities. In recent years, in the United Kingdom, the numbers of new cases of OA reported to SWORD have fallen by about 60%. Whether this demonstrates a real fall in disease incidence or is reflective of reductions in the size of the at-risk population, or of reporter fatigue, is unclear.

In secondary preventive strategies, immunologic tests—when feasible—can play a key role in detecting a pre-disease state. Assessing specific IgE sensitization has been performed routinely in several industrial sectors in the United Kingdom. For example, if an employee develops a positive prick test to platinum salt, she/he is relocated. In the detergent industry, the risk is claimed to be lower than previously but, due to its past history of sensitization and OA, IgE-based immunological surveillance is used routinely; rates of new sensitization are used to monitor the effectiveness of exposure controls. Such an approach has also been implemented on a smaller scale in bakers and laboratory animal workers. In the United Kingdom, routine surveillance of exposed employees is mandated when there is both exposure to a known respiratory sensitizer and a residual risk of OA. The term "residual risk" is usually considered in terms of exposure, but might usefully encompass settings with a high employee turnover or a relevant past history of cases. Methods used in surveillance are poorly studied, but the frequency of symptoms reported at surveillance is likely to underestimate the true prevalence (59). The action that should be taken for sensitized but asymptomatic workers is unclear. There are widespread concerns over surveillance, not least among employees, especially when, as is frequent, there is uncertainty over the clinical and employment outcomes of a "positive" finding. In certain settings, surveillance is a system which nobody involved really wants to succeed. For sensitized and symptomatic workers, avoidance of further exposure is recommended but often requires relocation.

Discussion

Prevention should include apprentices. Skin prick tests with common allergens at the beginning of apprenticeship have some predictive value for the development of sensitization to work-related allergens (60). A panel position document approved by the European Academy of Allergy, Asthma, and Clinical Immunology (61) focuses on prevention of WRA in young workers, including apprentices, and especially those with underlying allergy and/or asthma. Emphasis is given to education to promote workplace and personal protective measures and early recognition of work-related changes, rather than prevention of entry to apprenticeship or a job.

Web-based WRA educational materials for young workers have been developed in Ontario (62) and a web-based booklet for young individuals with asthma is being developed in Switzerland (www.suva.ch/fr/beratung_von_lehrlingen_mit_allergien.pdf), but these have not yet been formally evaluated to determine effectiveness as a supplement to workplace education. A secondary prevention study among autobody-shop workers exposed to diisocyanates in Quebec (63) showed that the workers with OA who were in the surveillance group by comparison with the other workers had an improved level of airway hyperresponsiveness and had approximately half the costs of compensation for permanent disability. Findings support reports that suggested benefit from the Ontario diisocyanate medical surveillance system (64).

Fractional exhaled nitric oxide level is a tool that can be considered in prevention programs. A study in bakery workers in South Africa (65, 66) found that allergen-specific IgE was the major determinant of fractional exhaled nitric oxide levels in bakery workers.

Theme 5: Other Work-Related Obstructive Airway Diseases

Presentation: M. Eisner

Discussion leaders: P. Blanc, S. von Essen, and K. Kreiss

Discussion participants: D. Lougheed, P. Blanc, D. Weissman, T. Sigsgard, P. Harber, and A. Cartier

Smoking is the most important cause of chronic bronchitis. However, among nonsmokers, the prevalence of COPD is 3 to 15%. Other risk factors include genetic factors, chronic asthma, passive smoking, air pollution, biomass smoke, and occupational exposures. Asthma increased the rate of lung function decline in the Copenhagen City Heart Study that included 17,000 subjects (67).

Working in dusty trades and occupations increases the risk of bronchitis and emphysema. An updated estimate published in 2009 provided a median estimate of personal attributable risk for COPD (defined by spirometry) of 15% in all subjects and 31% in nonsmokers (68); in addition, there was a risk of 15% for chronic bronchitis.

A statement issued by the American Thoracic Society (1, 69) and a state-of-the-art review (70) have addressed the occupational contribution to the burden of airway disease and nonsmoking causes of COPD. The risk is 2.4 (adjusted odds ratio [OR]) among nonsmokers comparing a worker group with and without occupational exposures (71). The risk is more important (adjusted OR of 18.4) by comparing a nonsmoking, nonexposed group with a smoking and exposed group.

Among subjects with α_1-antitrypsin deficiency, exposure to high levels of mineral dusts further worsens the extent of airflow limitation (72). Past exposure at work to vapors, gases, dust, or fumes was associated with adverse respiratory health outcomes (73). In a population-based study of 6,566 residents of New England, the prevalence of respiratory symptoms was 55% and respiratory symptoms were strongly associated with smoking, occupational exposures, and hay fever (74).

Another workplace factor is secondhand/sidestream/passive smoke. Several studies have shown an improvement in respiratory health in bartenders after smoking bans (75). Finally, bronchiolitis obliterans can be caused by exposure to diacetyl(2,3-butanedione) (76).

Discussion

The number of prevalent cases of COPD due to work was 1.6 million in the United States in 2001–2003, and the number of estimated deaths in 1997 was 5,000 to 24,000 (77, 78).

Practical implications include the need for occupational exposure history, not only a smoking history among patients with COPD. Preventive measures should focus on exposure reduction and, where needed, use of respiratory devices with good worker education. Suspicion is needed to detect new occupational causes for airway disease as demonstrated by the example of "popcorn worker's lung." ■

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Writing Committee
Susan M. Tarlo, M.B.B.S.
Jean-Luc Malo, M.D.

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Speakers, Discussants, and Other Formal Attendees:

X. Baur, M.D.; J. Beach, M.B.B.S., M.D.; M. Becklake, M.D.; D. Bernstein, M.D.; I. L. Bernstein, M.D.; P. Blanc, M.D., M.S.P.H.; P. E. Boileau, Ph.D.; S. Brooks, M.D.; P. S. Burge, M.B.B.S.; C. Carlsten, M.D.; A. Cartier, M.D.; N. Cherry, M.D.; M. Cruz, M.D.; R. Copes, M.D.; P. Cullinan, M.D.; A. Curran, M.B.B.S.; G. de Groene, M.D.; G. Delclos, M.D., M.P.H., Ph.D.; M. Eisner, M.D., M.P.H.; D. Fishwick, M.B.B.S.; H. Ghezzo, Ph.D.; P. Harber, M.D.; D. Heederik, Ph.D.; P. Henneberger, M.P.H., Sc.D.; D. L. Holness, M.D., M.H.Sc.; R. Hoy, M.B.B.S.; M. S. Jaakkola, M.D., Ph.D.; M. F. Jeebhay, M.D., Ch.B., Ph.D.; K. Kreiss, M.D.; F. Labrèche, M.D.; M. Labrecque, M.D., M.Sc.; K. L. Lavoie, Ph.D.; C. Lemière, M.D., M.Sc.; G. M. Liss, M.D.; D. Lougheed, M.D.; P. Maestrelli, M.D.; J.-L. Malo, M.D.; C. Mapp, M.D.; R. Merget, M.D.; G. Moscato, M.D.; X. Munoz, M.D., Ph.D.; B. Nemery, M.D., Ph.D.; K Pacheco, M.D., M.S.P.H.; G. Pala, M.D.; A. Peters; D. Prezant, M.D.; R. Qureshi, M.D.; S. Quirce, M.D. Ph.D.; C. Redlich, M.D., M.P.H.; M. Ribeiro, M.D., Ph.D; J. Sastre, M.D., Ph.D.; T. Sigsgaard, M.D., Ph.D.; F Silverman, Ph.D.; A. Siracusa, M.D., Ph.D.; S. M. Tarlo, M.B.B.S.; T. To, Ph.D.; O. Vandenplas, M.D.; S. von Essen, M.D.; J. Walusiak, M.D., Ph.D.; D. Weissman, M.D.

Additional Participants:

V. H. Arrandale, Ph.D.; S. D. Betschel, M.D.; S. Chiry; Y. Cloutier, B.Eng.; V. Comondore, M.D.; V. D'Alpaos, M.D.; P. Gomez; I. Foletti, M.D.; I. Kudla, H.B.Sc., M.H.Sc., C.I.H.; J. Lee, M.D.; A. Lau, M.D.; D. Miedinger, M.D.; J. Turcot, Ph.D.; H. Wong, M.D.; V. Wolski, M.D.; G. Wozniak, RN; J. Yuen, M.D.

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