

Staphylococci and staphylococcal superantigens in asthma and rhinitis: a systematic review and meta-analysis

C. Pastacaldi¹, P. Lewis² & P. Howarth³

¹Department of Paediatrics, Singleton Hospital, Swansea; ²Institute of Life Science, Swansea University, Swansea; ³University of Southampton, Southampton, UK

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Correspondence

Dr. Cinzia Pastacaldi MD FRCPCH MSc,
Department of Paediatrics, Singleton
Hospital, Sketty Lane, SA2 8QA Swansea,
UK.

Tel.: +44 (0)1792 285022

Fax: +44 (0)1792 285244

E-mail: cinzia.pastacaldi@wales.nhs.uk

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Abstract

Background: There is a need for new treatment options of allergic respiratory diseases based on a better knowledge of their pathogenesis. An association between bacterial products and allergic airway diseases has been suggested by the results of human and animal studies that describe a link between *Staphylococcus aureus* enterotoxins and atopic diseases. The aim of the systematic review is to assess the evidence for a role of *Staphylococcus aureus* enterotoxins, as an environmental risk factor, for the development and/or the severity of asthma and allergic rhinitis.

Methods: We performed a systematic review of controlled clinical studies in adults and/or children affected by asthma/early wheeze and/or allergic rhinitis. To be eligible, studies had to use reproducible methods to provide evidence of exposure to *S. aureus*, clinical outcome and disease severity.

Results: Ten studies, published between 2000 and 2007, fulfilled all eligibility criteria. Patients with asthma or allergic rhinitis showed an increased prevalence of positivity for measures of exposure to *S. aureus* in nine studies: differences were statistically significant ($P < 0.05$) in seven studies. In a meta-analysis of study results, patients with asthma were more likely than controls to have serum-specific IgE to *Staphylococcus aureus* enterotoxins (OR = 3.3, 95% CI: 1.6–7.1, $P = 0.002$); similarly, patients with allergic rhinitis were more likely than controls to test positive for local or systemic exposure to *Staphylococcus aureus* and/or its enterotoxins (OR = 2.4, 95% CI: 1.3–4.7, $P = 0.008$).

Conclusions: A potential role of *S. aureus* superantigens in allergic respiratory diseases is supported by results of this meta-analysis of clinical studies.

Asthma and allergic rhinitis are a worldwide health problem affecting people of all ages, ethnic groups and economic status. The increasing prevalence that characterized all the allergic diseases in the last 50 years seems now to be reaching a plateau in countries with higher prevalence, but is still increasing in areas with low or medium level of prevalence (1). Large studies such as ISAAC (International Study of Asthma and Allergies in Childhood) (2) and ECRHS (European Community Respiratory Health Survey) (3) estimated that there are about 200 million people worldwide affected by both asthma and rhinitis and that 500 and 300 million people suffer from rhinitis alone and asthma alone, respectively.

Asthma and allergic rhinitis are frequently associated in atopic subjects and they are considered as two different features of the same airway disease, requiring comparable preventative, diagnostic and therapeutic strategies (4). The

relationship between the nasal and lower airways is suggested by their functional complementarity (5), similar epidemiology (6) and common Th2 inflammatory process. This allergic inflammation is a consequence of the interaction between a genetic susceptibility and an environmental stimulus. Classically aeroallergens such as pollens, house dust mites allergens and animal allergens are considered to be the relevant environmental factors, but bacterial products have also been implicated.

Whilst bacterial stimulation of the immune system is classically related to stimulation of the innate immune system and Th1 and Th17 activation in the adaptive response, it is recognized that bacterial products, such as superantigens (7), may be linked to Th2-mediated inflammation (8). They are recognized to promote activation of T cells with cytokine release leading to B-cell activation and class switching to immunoglobulin E. *Staphylococcus aureus* (SA) is one of the most

common human bacterial pathogens producing enterotoxins that act as toxins as well as superantigens. The staphylococcal enterotoxins are a family of structurally related proteins comprising different serological types: e.g. *Staphylococcus* enterotoxins A, B, C, D, E (up to U) and toxic shock syndrome toxin-1. Most human *Staphylococcus aureus* have at least one gene encoding for the enterotoxins.

The first atopic condition to be associated with *Staphylococcus* superantigens was atopic eczema (9). Additional *in vitro* and *in vivo* studies have subsequently assessed the importance of SA exposure on the airways. These studies have demonstrated the potential for *Staphylococcus aureus* enterotoxins (SE) to induce an inflammatory response of the airways (10–13), an increase of sensitization to inhaled allergens (14–16) and a decreased T-cell sensitivity to steroids (17, 18). All these actions are relevant to disease expression and more severe airway disease. These observations support a research hypothesis that SA superantigens are one of the environmental risk factors for the development and/or the severity of asthma and allergic rhinitis. Therefore, we performed a systematic review to assess whether there is evidence of a higher prevalence of exposure or immune response to SA and SE in adult and children populations affected by allergic respiratory diseases, which would suggest a role of SA superantigens in their pathogenesis. Because of the nature of the research hypothesis, prospective randomized controlled trials would be unethical and in fact cannot be found in the literature; however, case-control studies of high quality would be appropriate to provide the evidence needed. Because sample sizes in case-control studies are often small, the benefits of a systematic review include the possibility of performing a meta-analysis to provide a more robust assessment of results.

Methods

Search strategy

Literature searches were performed on MEDLINE (1996–2007) and EMBASE (1980–2007) using the following search strategies: 'superantigen' or 'superallergen' or '*Staphylococcus aureus* enterotoxins' and 'asthma' or 'allergic rhinitis' or 'nasal polyposis'; 'Beta-lactam antibiotics' and 'asthma' or 'allergic rhinitis treatment'. The Cochrane Library was consulted by topic for 'airways' and 'infectious diseases' and searched using the following terms: 'superantigens' in title, abstract and keywords and '*Staphylococcus* superantigens' and 'asthma' or 'allergic rhinitis' with advanced search. The Web of Science was searched (for published and unpublished articles from 1970) using the terms: '*Staphylococcus* superantigens' and 'asthma' or 'allergic rhinitis' or 'nose polyps'. All searches were restricted to case-control studies involving humans and published in English. No limits of age or sex were applied.

In addition, Internet and hand searches were conducted, focusing on the following sources: web sites of relevant scientific organizations (BSACI, AAAAI, EAACI), case reports or case series, letters to the editor of relevant scientific journals, abstracts and proceedings of relevant conferences (BSACI,

AAAAI, EAACI). Google searches were conducted using the terms: 'Superantigens', '*Staphylococcus* superantigens', limited to the first ten relevant sites. A hand search of references from relevant publications and reviews was performed to identify additional articles of interest.

Study selection

Studies considered for the systematic review were case-control studies in adults and children affected by asthma/early wheeze and/or allergic rhinitis, investigating the association between exposure to SA or evidence of an immune response against SE and allergic respiratory diseases. To be eligible, studies had to use reproducible methods to provide evidence of exposure to SA, clinical outcome and disease severity (Table 1). Studies were excluded if they were uncontrolled or descriptive studies, if participating patients had other underlying chronic respiratory conditions, autoimmune disease or were on prophylactic antibiotic treatment.

Quality assessment, data abstraction and statistical analysis

Studies considered potentially eligible for inclusion in the systematic review were critically appraised using the Critical Appraisal Skills Programme (CASP) [Available at <http://www.caspp.org/>].

Table 1 Measures of exposure to SA, clinical outcome and disease severity considered acceptable for inclusion of studies in the systematic review

Measures of exposure to SA
Presence of SA, SAE or IgE specific to SAE in airways, measured or assessed in airways mucosal swabs, broncho-alveolar or nasal lavage or surgical samples
Presence of SA DNA in serum, assessed by PCR or T-TFLP
Determination of IgE-dependent immune reaction to SA superantigens in serum by measurement of levels of IgE specific to SAE
Evaluation of the effect of treatments with antibiotics (effective against <i>Staphylococcus aureus</i>) on allergic airway diseases.
Measures of clinical outcome or disease severity
Diagnosis and severity of asthma, or early wheeze for children population, assessed by a doctor or using approved guidelines
Diagnosis and severity of allergic rhinitis assessed by a doctor or using approved guidelines
Atopic status as defined by increased total IgE serum level
Sensitization to aeroallergens reported as presence of specific IgE in serum or positive SPT
Severity of allergic disease assessed by nasal symptoms scores, percentage of predicted FEV1, BHR, need of inhaled corticosteroids, serum ECP (Eosinophil Cationic Protein)
Immune system stimulation assessed by production of effector cells, cytokines, chemokines and mediators of allergic inflammation
Effect of antibiotics on allergic airway diseases assessed by improvement in symptoms score and decreased need of steroid treatment

www.cebm.net/index.aspx?o=1157 (accessed 1 June 2010)], and data abstraction tables were used to summarize key aspects including endpoints of the study, inclusion and exclusion criteria for the selection of cases and controls, measures of exposure to SA and SE, measures of outcomes, statistical methods, study patient disposition and baseline demographics, results of primary outcome with measure of variance and 95% confidence intervals (CI), results of secondary analyses.

Differences in the proportion of subjects positive for evidence of exposure to SA among cases and controls were analysed using a two-tailed Fisher's exact test if a statistical analysis had not already been performed in the study. Mantel-Haenszel statistics were used to calculate odds ratios with 95% CI in individual studies and in the meta-analysis. All statistical analyses were performed using SPSS version 19 (Chicago, Illinois, USA).

Results

Figure 1 illustrates the inclusion/exclusion process. Of 573 identified studies published between 2000 and 2007, 20 were potentially eligible; 10 of these fulfilled all eligibility criteria and were included in the systematic analysis.

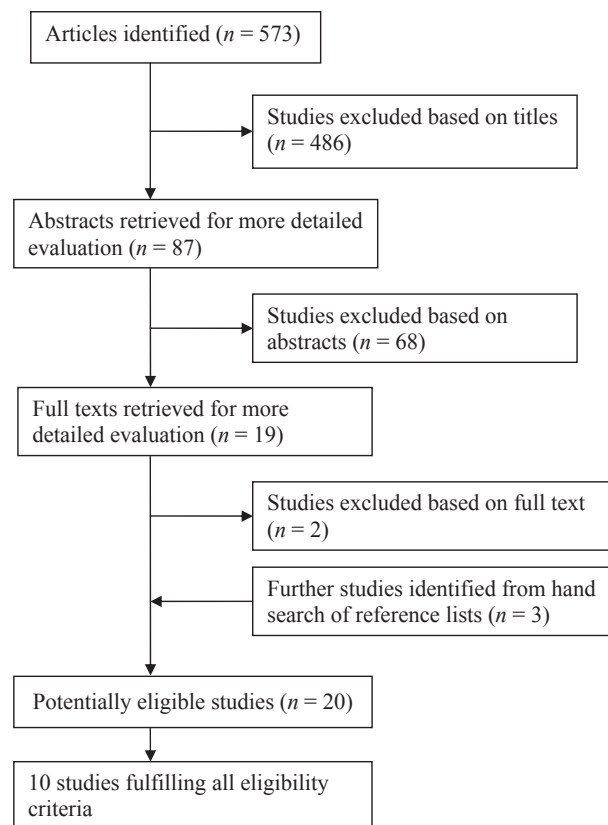


Figure 1 QUOROM diagram for study inclusion/exclusion. Adapted from Moher et al. (Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999;354:1896–1900).

The outcomes of interest were allergic rhinitis in four studies (19–22) and asthma/wheeze in three studies (23–25); three studies investigated both asthma and allergic rhinitis, of which two (26, 27) reported results separately for the two outcomes and one (28) cumulatively.

Asthma

Six studies (23–28) included asthma or early wheeze among their clinical outcomes of interest. Of these, one (25) was a prospective birth cohort study aiming to investigate the association of bacterial colonization of the hypopharynx with early wheeze and asthma in the first 5 years of life in children at risk of atopy. Colonization with SA was found in 61% of the children at 1 month and in 12% at 12 months of age but no significant association was found with asthma or early wheeze. Numerical data were not reported in the article, therefore *P*-values and odds ratios could not be calculated. In another study (28), the prevalence of sensitization to SE was significantly higher among subjects with allergic rhinitis and/or asthma compared with controls without allergic disease; however, the numbers of subjects with asthma, rhinitis or both conditions together were not reported separately, therefore *P*-values and odds ratios could not be calculated for each outcome.

The remaining four studies (23, 24, 26, 27) included a total of 360 patients with asthma and 493 controls. Asthmatic patients were identified on the basis of symptoms, FEV₁ results and need for treatment (23), bronchoprovocation test (24), validated questionnaire to collect patients' reported symptoms of asthma together with doctor's diagnosis of asthma and asthma treatment received (27) or recruited among patients attending an asthma clinic (26). The exposure to SA was evaluated through the detection in the serum of specific IgE against SE. Two of the studies (23, 27) used an SE mix consisting of SEA, SEB and TTST-1 and two assessed individual SE (SEA, SEB, SEC, SED and TTST-1 in the study by Rossi et al. (26) and SEA, SEB and TTST-1 in the study by Lee et al. (24)). One of the studies was conducted in children (27), one was restricted to adults (24) and the other two included both children and adults (23, 26).

All four studies found a significantly higher prevalence of IgE to SE among patients with asthma compared with controls, with odds ratios ranging from 1.9 to 16.4; in the meta-analysis (Fig. 2A), the pooled odds ratio was 3.3 (95% CI 1.6–7.1, *P* = 0.002).

The four studies also evaluated the association between exposure to SA and asthma severity. However, because different combinations of measure of disease severity were used, is not possible to report pooled results.

In the study by Bachert et al. (23), SE-specific IgE were more frequently found in patients with severe asthma (as assessed by measurement of FEV₁, need for inhaled or oral steroid treatment, and serum level of ECP) compared to controls (62% vs 13%, *P* = 0.01). In the study by Lee et al. (24), airway hyper responsiveness (as measured by methacholine bronchoprovocation test) was increased in SE-specific IgE-positive patients compared to SE-specific IgE-negative

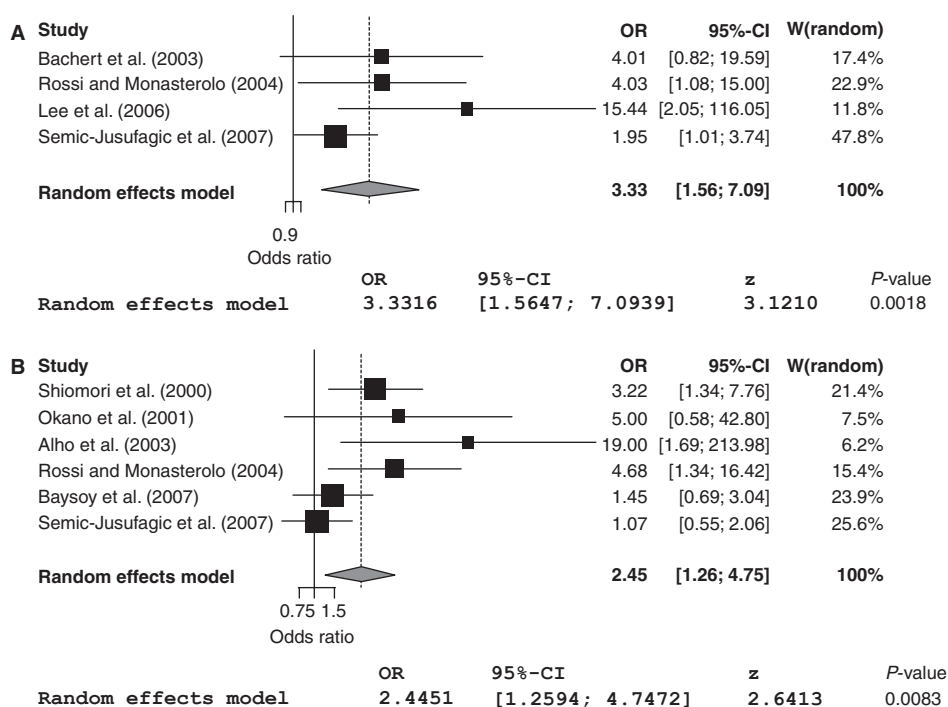


Figure 2 Forest plots of studies comparing the prevalence of exposure to SAE in patients with asthma (A) or rhinitis (B) and controls. In the graphs, black squares represent individual studies; the size of the squares is proportional to the number of subjects in

each study. Horizontal lines indicate 95% confidence interval ranges. Vertical dotted lines and diamond shapes represent pooled results with 95% confidence interval ranges.

patients ($P = 0.038$). Rossi et al. (26) evaluated the severity of asthma through assessment of serum ECP: no difference was found between SE IgE-positive and the SE IgE-negative patients with asthma. In this study, treatment with oral corticosteroids was not an exclusion criterion, which may have affected ECP levels. In the study conducted in children from birth to 5 years of age (27), wheezers with SE mix sensitization had significantly higher airway reactivity ($P = 0.04$) compared to wheezers without SE sensitization.

Allergic rhinitis

Allergic rhinitis was investigated as a clinical outcome in seven studies (19–22, 26–28). Three of the studies also investigated asthma: two of these reported data for the two outcomes separately (26, 27). The study by Lee et al. (28) found a significant prevalence of sensitization to SE in patients with asthma and/or allergic rhinitis compared to controls; however, the numbers of subjects with asthma, rhinitis or both conditions together were not reported separately, therefore P -values and odds ratios could not be calculated for each outcome.

The remaining six studies (19–22, 26, 27) included a total of 463 patients with allergic rhinitis and 608 controls. The diagnosis of allergic rhinitis was based on published guidelines (20), subjective symptoms and clinical examination (22, 26), validated questionnaire (27) and nasal symptoms score

(19, 21) and was confirmed by measurement of serum-specific IgE (20, 22, 26, 27) or by positive skin prick test (19, 21) to aeroallergens. The exposure to SA was assessed by detection of SA-positive culture in nasal tissue (22), serum-specific IgE to individual SE (SEA and SEB in the study by Okano et al. (20); SEA, SEB, SEC, SED and TTST-1 in the study by Rossi et al. (26) and SEB in the study by Alho et al. (21)) or SAE mix (27). Shiomori et al. (19) evaluated exposure to SA by culture of nasal swabs and detection of individual SE (A, B, C, D and TSST-1) in culture supernatant using rabbit-specific IgG. Three studies found a significantly higher prevalence of evidence of exposure or immune response to SA in patients with allergic rhinitis compared to controls (19, 21, 26). In the meta-analysis of combined results (Fig. 2B), the pooled odds ratio was 2.4 (95% CI 1.3–4.7, $P = 0.008$).

The association between severity of allergic rhinitis and prevalence of SE sensitization was investigated in four studies (19–21). Okano et al. (20) determined the severity of allergic rhinitis using nasal symptom scores. In 34 patients where the nasal scores were recorded, sensitization to SE was not correlated with the severity of allergic rhinitis. In the study by Rossi et al. (26), the severity of allergic rhinitis was determined assessing the levels of serum ECP. Patients with allergic rhinitis and sensitization to SE had higher serum ECP compared to allergic rhinitis patients who were not sensitized. Shiomori et al. (19) found that nasal symptoms scores among cases were significantly higher in SA

carriers compared to noncarriers ($P = 0.01$). In the study by Alho et al. (21), the severity of allergic rhinitis was determined through a CT scan score (CT scan of nasal passage and paranasal sinuses). Patients with allergic rhinitis and sensitization to SEB had a higher CT score compared to nonsensitized patients.

Search update

An update of the literature search was performed in May 2010 to verify whether any relevant study had been published after the completion of our systematic review and meta-analysis. This identified two articles comparing the presence of SE in upper airways of subjects with or without atopic disease. Wang et al. (29) assessed the presence of staphylococcal enterotoxins (SEA, SEB, SEC1-3, SED and TSST-1) by ELISA in nasal tissue samples from adult subjects with chronic rhinosinusitis ($n = 37$) and normal controls ($n = 12$); among 19 patients with chronic rhinosinusitis and atopy, nine (47.4%) tested positive for the presence of toxins, whilst there were no positive results in the control group. Shin et al. (30) performed immunoassays with ImmunoCAP in adenoid and tonsil tissue homogenates from 40 children (18 atopic and 22 nonatopic) undergoing adenotonsillectomy for reasons including rhinitis, recurrent infection and adenoid hypertrophy. The prevalence of IgE specific for SEA, SEB and TSST-1 in adenoid or tonsil tissues ranged between 61.1% and 11.1% among atopic children, whilst none of the nonatopic children tested positive.

Discussion

This systematic review of controlled clinical studies supports the hypothesis that SA superantigens play a role in allergic respiratory diseases. Most of the studies included in the review reported a higher prevalence of positivity for specific IgE against SE among atopic subjects compared with controls; however, individual studies were often based on small sample sizes and their results had wide confidence intervals. Our meta-analysis combined data from these studies, confirming in a more robust way that the probability of testing positive for evidence of exposure or an altered immune response to SA is significantly higher among patients with asthma (OR 3.3, 95% CI 1.7–7.1, $P = 0.002$) or allergic rhinitis (OR 2.4, 95% CI 1.3–4.7, $P = 0.008$) compared to controls. It must be highlighted however that there was considerable heterogeneity in how the studies available for our analysis defined exposure to SA and/or its superantigens, assessed outcomes and selected participants. Serum-specific IgE for SE where assessed in the majority of studies, with some variability in the types of enterotoxin investigated and the assays employed; other studies evaluated exposure in terms of positive cultures from respiratory mucosae, which however does not necessarily correlate with an immune response. Two studies (25, 27) identified cases and controls within birth cohort studies; the analyses however were limited

to the sub-populations of children providing valid data at the age of 5 years, i.e. excluding drop-outs. Finally, the age distribution of subjects varied among studies, and only a minority specifically addressed the paediatric population.

The clinical evidence gathered by our systematic review and meta-analysis is nonetheless consistent with preclinical data indicative of the potential relevance of staphylococcal superantigens and should encourage further research on the impact of staphylococcal superantigens on allergic respiratory disease (31, 32). Because of ease of measurement and the availability of established assays, most studies, as indicated, have focused on the ability of enterotoxins to act as conventional antigens and hence generate specific SE IgE. However, these enterotoxins can also act as superantigens by their ability to bind receptor structures found on T cells, B cells and major histocompatibility II (MHC II) proteins. In the case of the T-cell superantigens, the enterotoxin binds the variable β -chain ($V\beta$) of the T-cell receptor (TCR) and the class II MHC molecule outside the peptide-binding groove, on the surface of the antigen-presenting cell, thereby bypassing the need for processing by antigen-presenting cells. This enables SA to effectively modify the immune response to impair host defence and enable colonization. Activation of T cells via this route leads a clonal expansion of the specific enterotoxin-binding sub-sets (33) resulting in a skewing of the TCR $V\beta$ repertoire and a characteristic $V\beta$ profile 'signature'. Oligoclonal expansion of $V\beta 8$ and $V\beta 5.1$ in peripheral blood has previously been linked to allergy to house dust mite in adult asthmatics (34) and a significantly higher expression of T cells expressing $V\beta 8$ has been reported in a small group of poorly controlled asthmatics when compared to a combined group of well-controlled asthmatics and healthy controls (35). As superantigenic skewing of the $V\beta$ profile may not be specific to SE, because other bacteria such as streptococci for example may also generate superantigens (36), this data cannot be taken as direct evidence for SA involvement in disease pathogenesis. It is appreciated, however, that certain SE may target these specific $V\beta$ epitopes (37) and such data add to the collective information indicative of the relevance of superantigens to asthma and rhinitis. Furthermore, additional to this but beyond the scope of this meta-analysis is the substantial evidence that has been accumulated for the involvement of SA and SE in the pathogenesis of nasal polyposis (reviewed 38).

In summary, this meta-analysis supports a potential role of SA superantigens in the persistence and severity of asthma and allergic rhinitis. Larger studies could confirm the pathophysiological role of these superantigens and their association with disease severity. If superantigens are confirmed to modify, if not cause, allergic airways diseases then treatment studies should be considered: candidate therapeutic interventions include antibiotics active against SA, anti-IgE when SE-specific IgE are found in serum or respiratory tissues, antibodies against Th2-orientated cytokines to suppress the inflammatory process and, ultimately, vaccination therapy to prevent Staphylococcal infections (39).

Authors' contribution

All authors contributed to writing the manuscript and approved it.

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Conflict of interest

The authors have no conflict of interest to declare.

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