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Invited Review Article

Exacerbating factors and disease burden in patients with atopic dermatitis

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ABSTRACT

The number of patients with atopic dermatitis is on the rise worldwide, and Japan is no exception. According to recent estimates of the percentage of patients with atopic dermatitis in Japan by age, the majority of patients are between 20 and 44 years old. Because the peak age of onset of atopic dermatitis is during infancy, many patients may experience prolonged symptoms from infancy to adulthood. A prolonged clinical course also increases the burden of atopic dermatitis on affected patients. Decreased productivity due to work disruptions, reduced daily activity, higher direct medical costs, fatigue, and daytime sleepiness due to sleep disturbances are typical burdens on patients with atopic dermatitis. In order to reduce these burdens, it is necessary to shorten its clinical course and achieve long-term control without relying on medications, possibly by using avoidance or coping measures of aggravating factors. Typical aggravating factors of atopic dermatitis include irritant dermatitis, food allergy in children, sweating, and psychological stress in adults. Food allergy places a heavy burden on the quality of life of affected patients and their families. The effectiveness of educational interventions for sweating and psychological stress is unclear. We must also evaluate the economic burden and cost-effectiveness of interventions on the patient as aggravating factors to be addressed.

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Epidemiology and clinical course of atopic dermatitis

Atopic dermatitis (AD) is a common, chronic inflammatory skin disease in which patients experience repeated exacerbations and remissions.¹ Its worldwide prevalence is approximately 230 million people, varying by country and region.^{2,3} AD appears to be most prevalent in children; while adults are also affected, the age distribution of AD has changed over time. In Japan, the number of patients with AD has been increasing gradually in recent years. According to the results of a survey by the Japanese Ministry of Health, Labor, and Welfare, the number of patients with AD increased from about 350,000 in 2008 to about 510,000 in 2017, an increase of 160,000 patients.⁴ The total number of patients with urticaria and acne was estimated to be 250,000 and 200,000, respectively, in 2017⁴, suggesting that AD afflicts a larger proportion of the population than other common skin disorders. The age group percentages of patients with AD in Japan are currently 36% (0–19

years), 44% (20–44 years), 16% (45–69 years), and 4% (70 years and older), with the largest proportion in the 20–44 age group. Meanwhile, patients aged of 20–44 years account for 17%, 19%, and 16% of asthma, allergic rhinitis, and conjunctivitis patients, respectively, suggesting that population of AD in the age group with 20–44 years is larger than other common ailments.⁴

Currently, little is known about long-term clinical course of AD.⁵ According to the literature, most patients develop the disease within the first two years of life, experience episodic symptoms throughout childhood, and see improvements by adolescence. Studying the clinical course of AD has been particularly difficult because AD is a heterogeneous and intermittent disease. The clinical manifestations of AD vary from person to person, and there are often periods where symptoms and skin lesions are absent. With the growing interest in

AD, many longitudinal cohort studies have made it possible to estimate the changes in AD prevalence with the aging of a population by assessing the activity of AD in the same person at multiple time points. A systematic review and meta-analysis of studies found no significant differences in the prevalence of AD before and after childhood.⁶

We should consider the reasons for the high proportion of adult cases of AD. According to the results of a prospective, two-year

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follow-up study based in a variety of dermatology clinics, adult patients with AD older than 18 years of age experienced variable disease severity with time. Most patients also had variable lesion severity scores over time. A small number of patients had persistent moderate or severe lesions. Many patients with moderate lesions at baseline failed to achieve sustained remission of their disease.⁷

Kijima *et al.*⁸ and Matsumoto *et al.*⁹ conducted a retrospective allergy survey of college freshmen. The prevalence of AD among college freshmen in 2011 and 2018 was 16.5% (547/3,316) and 14.6% (392/2,688), respectively.^{8,9} The optical answer sheet questionnaire survey conducted in 2011 collected information on the age of onset, age at remission, and age at relapse of allergic disease (Fig. 1). The peak ages of onset for AD, bronchial asthma, and allergic rhinitis were during early infancy, early childhood, and at age 10, respectively. The peak age at remission was observed in early adolescence for bronchial asthma and in late adolescence for allergic rhinitis. AD dermatitis did not have a clear peak age at remission, but a relatively large number of cases were seen in both early childhood and adolescence. In terms of age at relapse, all three diseases showed a peak around the age of 18 years. Furthermore, the percentage of students who experienced remission at least once was 72.8% for males and 81.5% for females.⁹ In other words, a certain subset of patients with AD have never experienced remission. The group with a prolonged clinical course without remission and the group experiencing either relapse or onset after puberty may be responsible for the increase in the proportion of adolescent cases of AD.

The disease burden of atopic dermatitis

Socioeconomic burden

In Japan, a web-based cross-sectional survey was conducted in 2018 to evaluate the direct medical costs, self-medication costs (e.g. over the counter medications), and productivity losses of adult

patients with AD and to estimate the burden of disease according to disease severity for such patients. In addition, a survey of physicians was conducted to determine the amount of medical resources consumed according to disease severity.¹⁰ As a result, the burden of disease on adult patients with AD in Japan was estimated to be approximately 3 trillion yen, equivalent to 0.55% of Japan's gross domestic product in 2018. All components of the cost per adult patient with AD increased according to disease severity. The direct medical costs were estimated to be 450 billion yen/year based on a medical resource consumption survey of 100 Japanese physicians who regularly treated patients with AD.¹⁰

A survey conducted using the Work Productivity and Activity Impairment Questionnaire (WPAI)¹⁰ confirmed that even mild cases of AD, which account for 80% of all adult cases of AD, resulted in an approximate 10% decrease in performance during working hours. Patients with severe forms of AD accounted for only 2% of the total, but their performance loss during working hours was as high as 44%. For mild cases of AD, the annual productivity loss due to overall work impairment, including absenteeism and presenteeism, was estimated to be about 430,000 yen per patient and 1.2 trillion yen for Japan as a whole. Similarly, in cases of moderate AD, which accounted for 17.7% of all adult patients with AD, performance was reduced by about 25%, and the productivity loss per year was estimated to be about 1.3 million yen per patient, or about 792 billion yen for Japan as a whole (37% of the productivity loss of all adult patients with AD). In addition, when the cost burden per patient with a severe form of disease was compared with that of patients with moderate disease, direct medical costs increased 1.7 fold, productivity loss due to overall work impairment increased 1.3-fold, and productivity loss due to daily activity impairment increased 2-fold.¹⁰

When carefully comparing the disease burden across countries, in Europe, Eckert *et al.* found that in a WPAI study of 1,860 people with self-assessed AD,¹¹ the mean overall work productivity

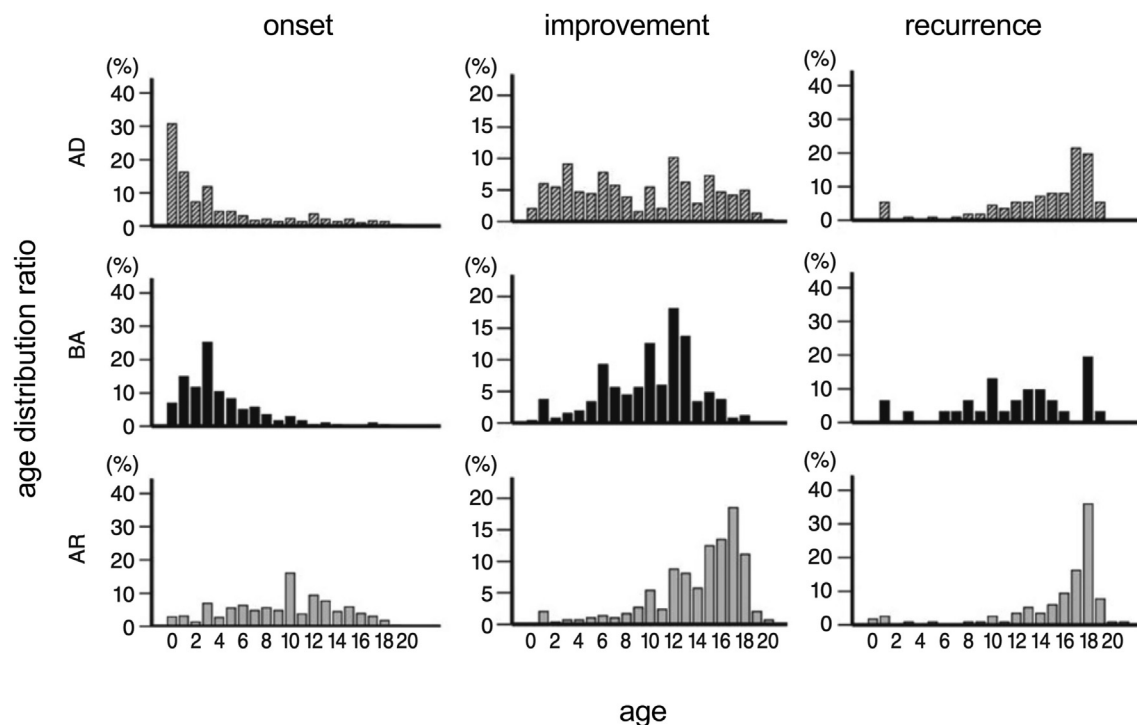


Fig. 1. Clinical course of allergic disease. The clinical course (onset, improvement, and recurrence) of atopic dermatitis (upper), bronchial asthma (middle), and allergic rhinitis (lower) was demonstrated. (Reprinted from reference 8 with permission.) Figures in x-axis indicates age (years old).

impairment and daily activity impairment of patients with confirmed AD were approximately 27% and 32%, respectively. In an online survey conducted by other researchers as part of the Japanese National Health and Welfare Survey in 2013, the mean overall work productivity impairment and daily activity impairment of patients with confirmed AD were 30.6% and 32.2%, respectively, which were not significantly different from the European results.¹² Furthermore, patients with a Dermatology Life Quality Index score of 10 or more (corresponding to severe and maximum severity) had a mean overall work productivity impairment and a daily activity impairment of 57.1% and 51.7%, respectively, suggesting that work disability rates increase with disease severity.¹¹ We previously evaluated the WPAI results of patients with AD who had visited the Department of Dermatology at Osaka University hospital or its affiliated hospitals and found that the average overall work productivity impairment was 40.4% and the daily activity impairment was 50.2%, which are relatively high disability rates¹³ (Fig. 2). Compared to other dermatoses, such as eczema/dermatitis, urticaria, pruritus, prurigo, and psoriasis, AD more severely impairs work place efficiency (Fig. 2). The reason for the relatively higher figures in this report may be that patients who receive care from university hospitals are more likely to have severe intractable AD.

A research group from the Japanese Ministry of Health, Labor, and Welfare surveyed the burden of disease in patients with AD from 2011 to 2013.¹⁴ The number of annual outpatient visits for AD was estimated at 890,000, the total cost of medical treatment was about 77.7 billion yen, and the drug prescription cost was about 15.4 billion yen, based on medical fee invoices. The average per capita cost of topical corticosteroids was high in dermatology clinics, but this may be due to the high number of patients with severe disease and the associated increase in drug use. In patients between 2 and 12 years of age, the drug cost of topical corticosteroids and moisturizing protection was higher than that of older ages. It is necessary to investigate how the financial burden on patients changes during the transition from pediatric to adult care.

Treatment burden

Previously, we evaluated the level of adherence to treatment in Japanese patients with AD who were enrolled in a monitoring

system.¹⁵ In this assessment, the level of adherence was quantified by using the Morisky Medication Adherence Scale-8 (MMAS-8), a structured self-report measure of medication-taking behavior.^{16,17} The mean scores for oral and topical medications were 4.6 and 4.2, respectively, compared with adherence levels of 6.2 and 5.4 for osteoporosis and asthma oral medications, respectively.^{18,19} Thus, Japanese patients with AD appear to have low adherence to both oral and topical medications. There is some supporting evidence on this issue: Krejci-Manwaring *et al.* reported low adherence to topical medications in children with AD,²⁰ and Feldman *et al.* reported that adherence in patients with AD across a wide age range was lower than that in patients with psoriasis and hand dermatitis.²¹ In these reports, adherence to topical medications was high on or around the day of the visit and declined rapidly soon after the visit.^{20,21} Thus, an important consideration is how to motivate patients to adhere to their treatment.

A barrier to medication adherence may be the amount of effort involved in administering the product. About 42% of patients with AD reported that the reason for discontinuing the use of topical medications was because it was inconvenient. Interestingly, this answer was also reported by 22.6% of patients as a reason for discontinuing their systemic medication.¹⁵ In other words, we must keep in mind that many patients with AD consider it more inconvenient and burdensome to apply a topical treatment than adhere to a systemic treatment.

Psychological burden

AD is known to be associated with intense itching, sleep disturbances, social embarrassment, and psychological distress.^{22,23} Among these effects, sleep disturbances are frequently caused by intense itching, which leads to daytime fatigue, irritability, cognitive impairment, and decreased capacity for exercise, significantly worsening the quality of life for patients.^{24–27}

Previous studies have shown that pediatric patients with AD have significantly poorer sleep quality, shorter sleep duration, more frequent and longer periods of awakening at night, and overall lower sleep efficiency.^{28–35} Adult patients with AD suffer from a variety of sleep disorders, including difficulty falling asleep, early morning awakening due to itching, poor sleep efficiency, excessive

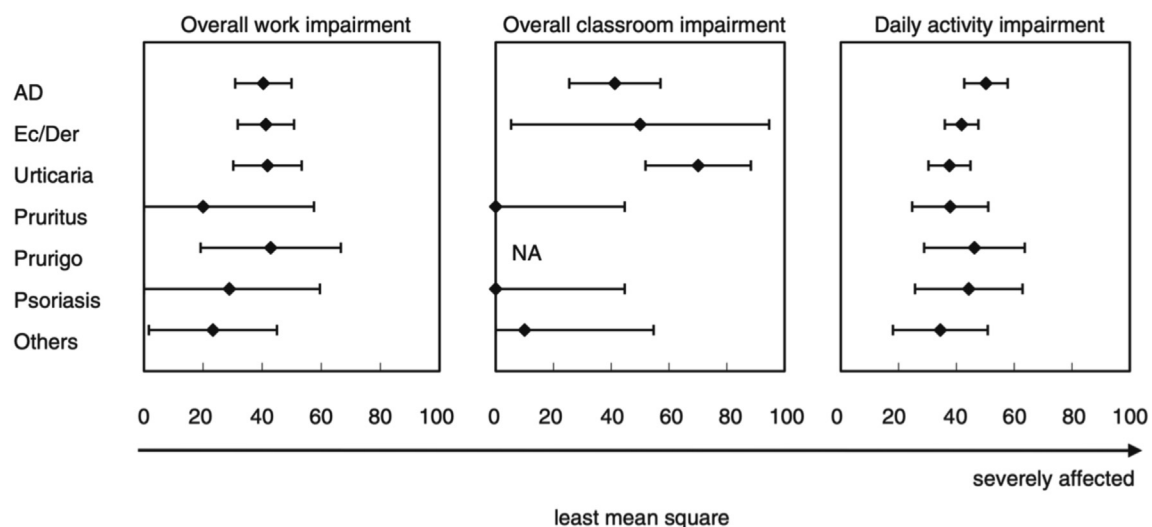


Fig. 2. Forest plots for each skin disease showing the degree of impairment as determined using a linear least-square method. Horizontal lines represent 95% confidence intervals. The rhomboid dot on the horizontal line indicates the point estimate. NA, not applicable. This study was conducted between April 2008 and March 2009. Patients with pruritic skin diseases ($n = 216$) were recruited, and the final number of valid responses was 206 (male: female = 93 : 113; mean age $\pm$ SD: 52 $\pm$ 20 years). Work, classroom, and daily productivity were assessed with the WPAI-AS instrument (score range, 0–100%; higher percentages indicate higher productivity). Reprinted from Reference 13 with permission.

fatigue, and persistent sleepiness. These effects result in daytime fatigue and insomnia at night. Adult patients with AD are more likely to have fair or poor overall health, regardless of whether they experience fatigue or sleep problems. However, those subjects with fatigue, sleep disturbances, and eczema are significantly more likely to self-report their health as fair to poor; they also tend to miss more days of work, sleep more, and see a doctor more frequently.²²

In 2013, data from the U.S. National Health and Wellness Survey were divided into an AD cohort and a non-AD cohort, and patient characteristics and outcomes were compared across cohorts and according to disease severity in terms of comorbidities, health-related quality of life (HRQoL), and outcomes.³ Compared with the non-AD cohort, patients with AD had a significantly higher prevalence of neuropsychiatric disorders, such as anxiety and depression. In addition, HRQoL was shown to be significantly lower in the AD cohort.

Shortening the clinical course of AD by reducing itching, improving sleep quality, providing psychological support, and rapidly inducing remission is important to decrease the psychological burden on patients with AD.

Impact of exacerbating factors

Many aggravating factors of AD are common in both childhood and adulthood, but some are unique to each. Major aggravating

factors include sweating and physicochemical stimuli, specific foods (commonly associated with pediatric AD), and psychological stresses (commonly associated with adult AD).^{1,9} During the development of food allergies, food antigens are thought to be involved in sensitization to the food via both transmucosal and transepidermal routes.³⁶ Because skin barrier disturbances and dermatitis can promote sensitization, it is necessary to keep the skin moisturized on a daily basis to minimize the severity of dermatitis.

AD can predispose patients to develop eczema, called atopic predisposition. Atopic predisposition includes a family history of allergic rhinitis, bronchial asthma, conjunctivitis, or AD or a predisposition to produce IgE antibodies.¹ In addition, the pathogenesis of AD consists of three main components: barrier dysfunction, itchiness, and inflammation, each of which has its own specific mechanism of action.¹ Barrier dysfunction of the skin is caused by a combination of abnormalities in both the stratum corneum and epidermis, resulting in increased permeability of the skin. As a result, water leakage from the skin occurs, allowing pathogens to penetrate and increasing the likelihood of irritant contact dermatitis. Heterozygous deletions in the filaggrin gene, whose product forms the keratinocyte framework and acts as a natural moisturizing factor via its degradation, have been found in some patients; these deletions have an allelic frequency of 5.65% in Japan.³⁷ Additionally, the tight junctions of the epidermis are prone to water leakage from the skin due to decreased expression of

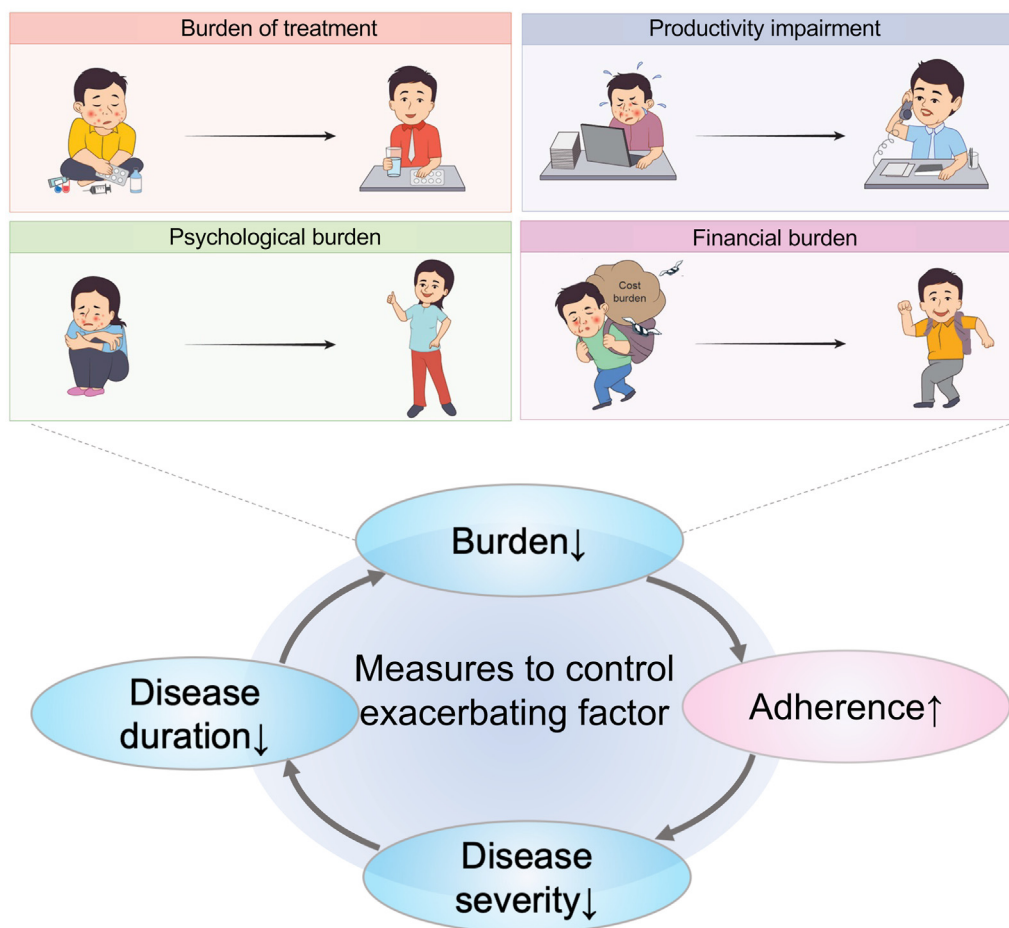


Fig. 3. Schema showing the relationship between disease burden and aggravating factors in atopic dermatitis. The disease burden includes the burden of treatment, psychological burden, productivity impairment, and financial burden. Reducing these burdens can improve patient adherence to treatment, reduce disease severity, and shorten disease duration. Measures to control exacerbating factors are expected to have a favorable impact on these burdens.

constituent claudin-1 proteins.^{38,39} Therefore, it is recommended that patients with AD use moisturizers on a daily basis to compensate for such barrier dysfunction. Moisturizers and other skin care products can be a financial burden for patients, and the task of applying them daily can also be a burden.

Food allergies can cause a variety of secondary effects. A history of food allergy increases the risk of developing AD by 8.7 fold, the risk of developing both AD and asthma by 12.5 fold, and the risk of developing AD, asthma, and allergic rhinitis by 32 fold.⁹ Management of food allergies by early skin care interventions is expected to prevent the progression of these risks. Food allergies adversely affect HRQoL.^{40–42} It is important to properly manage food allergies by food avoidance and, if necessary, instructions on the use of self-administered epinephrine injections. Fatal anaphylaxis has been shown to be associated with failure or delay in the administration of epinephrine.⁴³ Food allergies place a heavy burden on the HRQoL of patients and their families. Previous studies have shown that patients with a higher number of food allergies have a lower HRQoL than those with a lower number of food allergies because a higher degree of care is required to avoid food allergens.^{44–46} Among children with food allergies, those with cow's milk and egg allergies have a lower HRQoL than those with allergens that are easier to avoid.^{47,48} Poor HRQoL specific to food allergies has been reported to be worse among children and caregivers with a history of severe allergic reactions to food, those with more severe symptoms during previously reported allergic reactions to food, and those with a history of epinephrine use.^{45,46,49} In addition to the paucity of effective treatments, the stress of daily food allergy management often affects family relationships and limits social activities, ultimately leading to a decline in food allergy-related QoL.⁵⁰ In addition to its impact on physical and psychological health, food allergies have been found to impose a considerable economic burden at both the individual and societal levels.⁵¹ A 2019 systematic review of 11 studies addressing the economic burden of food allergies concluded that a major contributor was lost opportunity costs at the individual and household level.⁵²

AD also causes abnormalities in physiological functions such as vascular responses and sweating. In particular, there is an alteration in acetylcholine responsiveness, abnormal vascular responses, and decreased sweating, leading to increased skin temperature, inflammation, and dry skin, which increases the likelihood for infection, itching, and worsening dermatitis.^{53–57} As itching tends to occur during exercise and bathing, and upon exposure to stress, patients tend to avoid activities that make them sweat or cause blood vessels to dilate. Whether this is a psychological or socioeconomic burden for patients needs to be examined in the future.

Conclusions

The severity of AD and its prolonged disease course increase the burden of disease (Fig. 3). In order to reduce this burden on patients, the goal of treatment is to reduce the severity of disease for a long duration. In addition, even during long-term control, increasing adherence to regimens for therapeutic drugs and skin care will reduce the burden on patients. In order to achieve long-term control without depending on medications, countermeasures against aggravating factors (irritant dermatitis, childhood food allergies, sweating, and psychological stress in adults) are necessary. The burden of these exacerbating factors on patients is an important issue that needs to be investigated in the future.

Conflict of interest

The authors have no conflict of interest to declare.

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