

The combined diagnosis of allergic and irritant contact dermatitis in a retrospective cohort of 1000 consecutive patients with occupational contact dermatitis

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Summary

Background. The diagnosis of combined allergic and irritant contact dermatitis is an accepted subdiagnosis for hand dermatitis, and it is often considered in a patient with contact dermatitis, a positive and relevant patch test result, and wet work exposure. We therefore hypothesize that it is arbitrary for wet work exposure to be taken into consideration in a patient with newly diagnosed relevant contact allergy. Furthermore, an overestimation of the diagnosis will probably occur if the criteria for wet work exposure are applied correctly, as many occupations have an element of wet work.

Objectives. To find the statistically expected number of combined allergic and irritant contact dermatitis cases in 1000 patients, and to evaluate the diagnostic criteria for the diagnosis.

Methods. One thousand consecutive patients with occupational contact dermatitis from a hospital unit in Denmark were assessed.

Results. The expected number of cases with the diagnosis of combined allergic and irritant contact dermatitis was 0.33%, as compared with the observed number of 6.4%. Females occupied in wet occupations were often diagnosed with combined allergic and irritant contact dermatitis ($p < 0.005$).

Conclusion. The diagnosis of combined allergic and irritant contact dermatitis should be used critically to avoid misclassification, and possible criteria for the diagnosis are proposed.

Key words: allergic contact dermatitis; classification; diagnosis; epidemiology; hand eczema; irritant contact dermatitis; occupational.

Hand dermatitis is a common disease in Europe, with a 1-year prevalence in the background population of ~10% (1). In Denmark, hand dermatitis is the most frequently recognized occupational disease (2), and, in various high-risk occupations, the incidence rate of

occupational contact dermatitis is as high as 100 cases per 10 000 workers per year (3–5).

No generally accepted classification system for hand dermatitis exists. However, the European Environmental and Contact Dermatitis Research Group has presented a classification system for hand dermatitis that includes the subdiagnosis of combined allergic and irritant contact dermatitis (6). Combined allergic and irritant contact dermatitis is based on the definition on each of the diagnoses of allergic contact dermatitis and irritant contact dermatitis (6, 7).

The clinical presentation of contact dermatitis caused by either contact allergy or irritation

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cannot, with the present knowledge, be used to discriminate between allergic or irritant contact dermatitis (8). Therefore, the diagnoses are classified by the existence of dermatitis with a temporal relationship with an exposure (7).

The diagnosis of allergic contact dermatitis is made on the basis of a positive patch test result and the ascertained exposure to the contact allergen in question in a way that fully or partly explains the dermatitis (7). Systematic studies of quantitative exposure assessment of contact dermatitis, supported by experimental dose–response studies on sensitized individuals, support this definition of allergic contact dermatitis (9–12). Moreover, experimental studies have found that real-life repeated allergen exposures can elicit allergic contact dermatitis.

Irritant contact dermatitis, on the other hand, is diagnosed by significant exposure to known irritants and a temporal relationship between exposure to irritants and the dermatitis (7), often with a negative patch test result or with no temporal relationship between the contact allergen and the dermatitis.

In recent years, the definition of irritant contact dermatitis has been reviewed, and is now applied to patients with contact dermatitis when they fulfil the criteria for wet work: wet work for > 2 hr daily or frequent hand washing > 20 times daily (13, 14). The matter of temporality still applies; a temporal relationship between the contact dermatitis and the irritant exposure must exist.

The definition of the diagnosis of combined allergic and irritant contact dermatitis is based on the definition of each of the diagnoses. The question of temporality in the diagnosis of combined allergic and irritant contact dermatitis is complex, and when temporality in a combined diagnosis composed of two definitions is discussed, an inherent contradiction appears, as both the temporal relationship between the allergen and development of the dermatitis and that between the irritant and development of the dermatitis are used.

Our hypothesis is that the diagnosis of combined allergic and irritant contact dermatitis, owing to its inherent contradiction in temporality between two responses (contact allergy and irritation) and only one clinically presented dermatitis, is a diagnosis that should be critically used by the clinician, as the definition of it is too weak. At present, it is particularly unclear when and to what degree the wet work criteria should influence the diagnostic work-up in a patient with a relevant positive patch test result. Therefore, it may be arbitrary for the treating clinician to take the exposure to wet work into consideration in a patient with a newly diagnosed contact allergy (e.g. to gloves), and this can introduce random errors, and thereby potentially result in an incorrect diagnosis.

The aim of the present study was to present the demographics for the diagnosis of the combined allergic and irritant contact dermatitis, to find the statistically expected number of combined allergic and irritant contact dermatitis diagnoses in a cohort of 1000 consecutive patch tested patients, and to evaluate the diagnostic criteria for the diagnosis of combined allergic and irritant contact dermatitis.

Materials and Method

Study population

The present analysis is based on a previously presented study population, and has been described in detail elsewhere (4). The study population comprised 1000 consecutive cases of occupational contact dermatitis diagnosed at the Department of Dermato-Allergology at Gentofte University Hospital, Denmark, between 1 September 2003 and 31 December 2010.

Information available from the database included diagnosis, information concerning the MOAHLFA index, and patch test results.

Diagnosis

All patients were given a final diagnosis at the time of patch testing, according to the published recommendations (6, 7, 15). The subdiagnoses of protein contact dermatitis and atopic dermatitis with no irritant or allergic contact dermatitis were not included in the analysis. The following subdiagnoses were used: allergic contact dermatitis, irritant contact dermatitis, and the diagnosis of combined allergic and irritant contact dermatitis. Patients with known atopic dermatitis and one of the above three diagnoses were included. All patients had occupational contact dermatitis.

The diagnosis of (occupational) allergic contact dermatitis was made if the following existed: (i) positive patch test reaction to a substance present at the workplace, (ii) skin contact with the substance, (iii) and sufficient exposure intensity and duration to explain the dermatitis (6, 7, 16).

The diagnosis of (occupational) irritant contact dermatitis was made if allergic contact dermatitis could be excluded by a negative patch test result and if the patient had frequent skin contact with known irritants, and performed frequent hand washing (>20 times daily) or wet work (>2 hr daily) (6, 7, 13, 14).

The diagnosis of combined allergic and irritant contact dermatitis was based on an individual judgement by the treating dermatologist.

Patch testing

Patch testing was performed with the European baseline series according to the recommendations of the International Contact Dermatitis Research Group (ICDRG) (15).

In the entire test period, patch tests were performed with Finn Chambers® and Scanpor® tape applied to the upper back. The occlusion time was 48 hr, and readings were performed at D2, D3/D4, and D7, in accordance with the recommendations of the ICDRG (15). Reactions of strength 1+, 2+ and 3+ were interpreted as positive responses. Irritant reactions, doubtful reactions and negative reactions were interpreted as negative responses. In cases of retesting, only patch test data obtained at the first visit were used in the analysis (15).

Occupational classification

Occupation was coded according to the Danish International Standard Classification of Occupations (DISCO-88) at the time of patch testing. The DISCO-88 codes were aggregated to a new occupational classification. This new occupational classification has been described previously (4).

The incidence rates for the diagnosis of combined allergic and irritant contact dermatitis according to occupation were calculated on the basis of all employees in each occupation in the capital region of Denmark, as of 1 January 2010.

Statistical analyses

The data were processed with SPSS™ (SPSS Statistics, Chicago, IL, USA; IBM PASW Statistics) for Windows™, edition 19.0. Analyses were performed on prevalence, and the Pearson chi-square test was used to compare categorical characteristics.

For the analysis of the expected number of cases with the diagnosis of combined allergic and irritant contact dermatitis, the following was assumed: each employee within an occupation, regardless of age and atopic dermatitis, had the same probability of developing occupational contact dermatitis. For the purpose of finding the expected number of cases with combined allergic and irritant contact dermatitis, all cases diagnosed with combined allergic and irritant contact dermatitis were counted as only having allergic contact dermatitis, as described previously (4). Furthermore, it was assumed that allergic contact dermatitis and irritant contact dermatitis occurred independently of each other.

Within each occupational group, an employee had an incidence rate of allergic contact dermatitis, P_A , and an

incidence rate of irritant contact dermatitis, P_I . Thus

$$P_* = P_I - P_A P_I$$

$$P_I = P_* / (1 - P_A)$$

where P_I is the incidence rate of irritant contact dermatitis in the other trades.

Assuming that allergic contact dermatitis and irritant contact dermatitis are independent events, it is possible to estimate the number of expected events with combined allergic and irritant contact dermatitis as

$$P_I P_A \text{Total}$$

where Total represent the total number of employees in an occupation.

Results

In total, 1000 patients (618 females and 382 males) were included (4). Table 1 shows the occupational classification and incidence rates for patients diagnosed with combined allergic and irritant contact dermatitis. The observed proportion of patients diagnosed with combined allergic and irritant contact dermatitis was 6.4% ($n = 64$).

The sex ratio (female/male) for the group of patients diagnosed with combined allergic and irritant contact dermatitis was 3.6 (50/14), and that for the group of patients diagnosed with either an irritant or allergic dermatitis was 1.5 (568/368) (controls) ($p < 0.005$).

No difference in mean age was observed between the group of patients diagnosed with combined allergic and irritant dermatitis [40.0 years; 95% confidence interval (CI) 36.6–43.3] and the control group (39.3 years; 95% CI 38.4–40.1).

Statistical analysis made it possible to estimate the expected number of combined allergic and irritant contact dermatitis diagnoses for numerous occupations for both females and males (Tables 2 and 3). Overall, we calculated the expected numbers of combined allergic and irritant contact dermatitis diagnoses in a retrospective cohort of 1000 patients as 2.72 for females and 0.54 for males; in total, 3.26 (0.326%).

Discussion

This study presents the demographics of occupational contact dermatitis cases, and attempted to find the statistically expected number of cases diagnosed with combined allergic and irritant dermatitis within a retrospective cohort of 1000 consecutive patients.

Table 1. The distribution of occupation according to sex; the incidence rates for the diagnosis of combined allergic and irritant contact dermatitis were calculated

	Female	Male	Total (%)	No. of female employees in the capital region of Denmark	Incidence rate for females per 10 000 workers per year	No. of male employees in the capital region of Denmark	Incidence rate for males per 10 000 workers per year
Bakers	3	0	3 (4.7)	231	18.6	676	0.0
Blacksmiths	0	2	2 (3.1)	–	–	3611	0.8
Cleaning personnel	10	1	11 (17.2)	10 694	1.3	5784	0.2
Cooks	7	1	8 (12.5)	3567	2.8	2892	0.5
Nursery school teachers	2	0	2 (3.1)	19 708	0.1	–	–
Dental surgery assistants	1	0	1 (1.6)	2150	0.7	–	–
Dentists	0	2	2 (3.1)	695	0.0	353	8.1
Hairdressers	6	0 (1*)	6 (10.9)	1395	6.1	–	–
Mechanics	0	2	2 (3.1)	–	–	2442	1.2
Nurses and nursing assistants	13	0	13 (20.3)	42 833	0.4	–	–
Office workers	1	0	1 (1.6)	30 305	0.0	7996	0.0
Painters	0	1	1 (1.6)	–	–	–	–
Shop assistants	1	0	1 (1.6)	20 690	0.1	–	–
Others	6	5	11 (17.2)	–	–	–	–
Total	50	14	64	–	–	–	–

*Aggregated into 'Others' for males.

Table 2. The statistically expected number of females with the diagnosis of combined allergic and irritation contact dermatitis; the calculation is based on the observed incidence rates of allergic contact dermatitis and irritant contact dermatitis

	No. of employees in the capital region of Denmark	ICD	ACD	P_*	P_I	P_A	Expected ACD + ICD	Observed ACD + ICD
Beauticians	163	6	1	0.037	0.037	0.006	0.04	0
Bakers	231	7	8	0.030	0.031	0.035	0.25	3
Butchers	174	2	2	0.011	0.012	0.011	0.02	0
Cleaning personnel	10 694	31	36	0.003	0.003	0.003	0.10	10
Cooks	3567	33	28	0.009	0.009	0.008	0.26	7
Dental surgery assistants	2150	9	19	0.004	0.004	0.009	0.08	1
Dentists	695	5	2	0.007	0.007	0.003	0.01	0
Hairdressers	1395	44	55	0.032	0.033	0.039	1.81	6
Kitchen workers	3376	4	0	0.001	0.001	0.000	0.00	0
Laboratory technicians	5651	3	7	0.001	0.001	0.001	0.00	0
Machine operators	865	3	3	0.003	0.003	0.003	0.01	0
Nurses and nursing assistants	42 833	57	51	0.001	0.001	0.001	0.07	13
Nursery school teachers	19 708	13	8	0.001	0.001	0.000	0.01	2
Office workers	30 305	17	27	0.001	0.001	0.001	0.02	1
Painters	360	1	5	0.003	0.003	0.014	0.01	0
Physicians	2854	7	7	0.002	0.002	0.002	0.02	0
Shop assistants	20 690	3	4	0.000	0.000	0.000	0.00	1
Others	295 672	47	63	0.000	0.000	0.000	0.01	6
Total	–	292	326	–	–	–	2.72	50

ACD + ICD, expected number of cases with the diagnosis of combined allergic and irritant contact dermatitis; ACD, allergic contact dermatitis; ICD, irritant contact dermatitis; P_* , incidence rate of irritant contact dermatitis; P_I , incidence rate of irritant contact dermatitis in the other trades; P_A , incidence rate of allergic contact dermatitis.

The expected number of cases with combined allergic and irritant contact dermatitis was 3.3 (0.33%), and the actual observed number was 64 (6.4%). With this calculation, we wanted to bring a focus on the diagnosis of combined allergic and irritant contact dermatitis.

The diagnosis of allergic contact dermatitis is well defined (6, 7), whereas the diagnosis of irritant contact dermatitis is less well studied, and no routine test or biomarker for irritancy exists. In a historical perspective, irritant contact dermatitis was a diagnosis by exclusion

Table 3. The statistically expected number of males with the diagnosis of combined allergic and irritant contact dermatitis; the calculation is based on the observed incidence rates of allergic contact dermatitis and irritant contact dermatitis

	No. of employees in the capital region of Denmark	ICD	ACD	P_*	P_I	P_A	Expected ACD + ICD	Observed ACD + ICD
Bakers	676	10	6	0.015	0.015	0.009	0.09	0
Blacksmiths	3611	9	8	0.002	0.002	0.002	0.02	2
Bricklayers	1943	6	4	0.003	0.003	0.002	0.01	0
Butchers	803	3	1	0.004	0.004	0.001	0.00	0
Carpenters	3736	6	5	0.002	0.002	0.001	0.01	0
Cleaning personnel	5784	8	10	0.001	0.001	0.002	0.01	1
Cooks	2892	24	13	0.008	0.008	0.004	0.11	1
Dentists	353	0	1	0.000	0.000	0.003	0.00	2
Electricians	6277	8	8	0.001	0.001	0.001	0.01	0
Kitchen workers	2385	2	3	0.001	0.001	0.001	0.00	0
Locksmiths	441	4	3	0.009	0.009	0.007	0.03	0
Machine operators	2921	17	9	0.006	0.006	0.003	0.05	0
Manual workers	13 091	10	5	0.001	0.001	0.000	0.00	0
Mechanics	2442	22	12	0.009	0.009	0.005	0.11	2
Nurses and nursing assistants	4941	4	0	0.001	0.001	0.000	0.00	0
Nursery school teachers	5279	1	3	0.000	0.000	0.001	0.00	0
Office workers	7996	5	6	0.001	0.001	0.001	0.00	0
Painters	1655	8	12	0.005	0.005	0.007	0.06	1
Physicians	2730	6	3	0.002	0.002	0.001	0.01	0
Plumbers	3567	7	3	0.002	0.002	0.001	0.01	0
Others	395 475	57	50	0.000	0.000	0.000	0.00	5
Total	468 998	217	165	–	–	–	0.54	14

ACD + ICD, expected number of cases with the diagnosis of combined allergic and irritant contact dermatitis; ACD, allergic contact dermatitis; ICD, irritant contact dermatitis; P_* , incidence rate of irritant contact dermatitis; P_I , incidence rate of irritant contact dermatitis in the other trades; P_A , incidence rate of allergic contact dermatitis.

(17). The diagnosis was applied to a contact dermatitis with a considerable duration, and only when careful patch testing had failed to reveal a contact allergy explaining the contact dermatitis (17). In recent years, irritant contact dermatitis has become a diagnosis defined by significant exposure to known irritants and the temporal relationship between the exposure and the dermatitis (7). The clinician often suggests a diagnosis of irritant contact dermatitis if one of the following wet work criteria exist in a patient with dermatitis: wet work for > 2 hr daily, or hand washing > 20 times daily (wet–dry cycles) (13, 14).

The wet work criteria were initially presented for occupational dermatologists in Germany to enhance preventive actions and to ensure appropriate legal procedures when notified occupational skin diseases were evaluated (13, 14). The wet work criteria are primarily based on experimental studies and epidemiological data, for example the increased risk of developing dermatitis in a selected group of hairdressing apprentices exposed to wet work for > 2 hr daily (13, 18). There is no internationally accepted definition of wet work, but the German definition is widely used for both practical and working reasons in European countries (13, 19).

However, the use of the wet work criteria as diagnostic criteria for irritant contact dermatitis is in fundamental conflict with medical tradition: causality with reference to the relationship between an exposure and an effect. Wet work mediates minor irritant skin traumas, for example dry skin with a risk of the development of irritant contact dermatitis, but wet work as such is not prognostic for irritant contact dermatitis (13, 20). Therefore, it is problematic that the wet work criteria, for practical reasons, are used as diagnostic criteria at the same level as a relevant positive patch test result is the basis for diagnosing allergic contact dermatitis. The use of wet work as diagnostic indication of irritant contact dermatitis will, to some degree, result in an overestimation of the prevalence of irritant contact dermatitis if no meticulous patch testing and systemic stepwise exposure assessment have been conducted prior to the assignment of the diagnosis of irritant contact dermatitis (21).

Patients with contact dermatitis are often exposed to both irritants and allergens in an occupational setting. Up to 40% of all occupations can be classified as having excessive contact with irritants (20). Therefore, the component of irritancy is difficult to assess in a patient with contact dermatitis and a relevant positive patch test result.

Patients with a contact dermatitis and with a relevant patch test result could, in theory, be assigned the diagnosis of combined allergic and irritant contact dermatitis when they are employed in an occupation with excessive contact with irritants (20, 22). An example is newly diagnosed thiuram mix sensitization in a nurse resulting from extensive use of gloves and many wet–dry cycles throughout the day: it may be arbitrary for the exposure to wet work to be taken into consideration by the treating clinician. At first glance, and based on the diagnostic criteria for wet work, the nurse should be assigned the diagnosis of combined allergic and irritant contact dermatitis.

The diagnosis of combined allergic and irritant contact dermatitis therefore has inherent contradictions, as it is defined by two sets of diagnostic criteria: a relevant positive patch test result and exposure to wet work. In a patient exposed to both allergens and irritants, and who fulfil the diagnostic criteria for both allergic contact dermatitis and irritant contact dermatitis, the question of temporality becomes blurred, as the definition of the combined diagnosis is weakly defined. At present, no satisfactory diagnostic tool exists for diagnosing the irritant component in a patient with occupational contact allergy (7, 13, 14).

In our study population, the prevalence of combined allergic and irritant contact dermatitis was found to be 6.4%, as compared with former estimates in various clinical populations of 9.4–21% (3, 6, 22–24). Such data are typically based on multicentre studies in which the participating clinicians have had the option to use the diagnosis of combined allergic and irritant contact dermatitis, often without making the judgement of whether contact allergy or irritation was the predominant aetiological factor, and without any attention to temporality.

To summarize, the observed frequency of combined allergic and irritant contact dermatitis depends on the study population and on the quality of diagnostic work-up in ways that the authors of this analysis think are problematic.

In this analysis, wet work was the culprit of combined allergic and irritant diagnosis, as cleaning, health-care, cooking and hairdressing were frequent occupations, which correlates with a prior Danish study (24). To our knowledge, this is the first study presenting data obtained in a retrospective cohort on incidence rates for occupations diagnosed with combined allergic and irritant contact dermatitis.

The demographics for combined allergic and irritant contact dermatitis show a sex ratio of 3.6, which is not in line with other studies that have found a sex ratio for hand eczema of 1.5–2.0 (3, 5, 6, 24, 25). The higher frequency of combined allergic and irritant contact dermatitis in females probably reflects the high proportion of females in wet occupations who fulfil the criteria for wet work and excessive use of protective gloves. It is a paradox that the appropriate and recommended use of protective gloves is indirectly used as diagnostic criterion for the diagnosis of irritancy, as wet–dry cycles increases with the excessive use of protective gloves. This inherent weakness of the diagnostic criteria for irritant contact dermatitis will probably lead to an overestimation of irritant contact dermatitis (16), and thereby also an overestimation of combined allergic and irritant contact dermatitis. The relatively high sex ratio for the diagnosis of combined allergic and irritant contact dermatitis could also be explained by the fact that the treating dermatologist is not as focused on irritants in male-occupied industries as on irritants in wet occupations, for example work with metalworking fluids in comparison with frequent hand washing. Moreover, a substantial percentage of workers in the metalworking industry also perform frequent hand washing (22).

The diagnosis of combined allergic and irritant contact dermatitis, with its inherent contradiction regarding temporality, should therefore be used critically. Possible future diagnostic criteria for combined allergic and irritant contact dermatitis are shown in Table 4. The diagnosis of combined allergic and irritant contact dermatitis should be made according to the definition of each of the diagnoses, but, by considering the dermatitis over a

Table 4. Future diagnostic criteria for the diagnosis of combined allergic and irritant contact dermatitis

Allergic contact dermatitis	Irritant contact dermatitis
Still assigned on the basis of a positive patch test result and ascertained exposure to the contact allergen in question (7)	Significant exposure to known irritants, e.g. high-risk occupations
	Wet work criteria (8, 13, 14) should be used critically in the diagnostic procedure, and only when: There is a temporal relationship between the exposure to the contact allergen and the dermatitis The dermatitis persists for a considerable duration, and the exposure to the contact allergen has been successfully avoided for a time period of 3–6 months

time period, the matter of temporality between the irritant exposure and the dermatitis can be pointed out (Table 4).

In the statistical calculation of the expected number of patients with combined allergic and irritant contact dermatitis, the quality of the skin barrier (phenotype and genotype) was not taken into consideration (Tables 2 and 3). Furthermore, it was assumed that irritant and allergic contact dermatitis are not positively correlated, which is an exaggeration. Contact allergy and skin irritancy are, both in theory and clinically, positively correlated. In acute skin irritancy, the skin often releases proinflammatory cytokines, causing and amplifying the inflammatory reaction. This leads to vasodilatation and infiltration of, for example, lymphocytes, eosinophils, macrophages and T cells at the site of skin irritation as part of a relatively fast and innate skin response (26). Regarding pathogenesis, the allergic response has some pathogenic features in common with the innate irritant response (27, 28). Whether an allergic response to a hapten is induced and subsequently elicited probably depends on a poorly defined 'danger signal' (29). A 'danger signal' or cutaneous irritancy is needed to induce sensitization when a contact allergy is developed; and it is also possible that the irritation enhances the allergic response (30–32). It could therefore be postulated that daily and relatively frequent exposure to irritants would trigger these 'danger signals' in the skin, which would induce contact allergy instead of a tolerance response when the skin is exposed to a hapten. Furthermore, the hapten often produces both the antigenic signal and the irritant signal as a result of its inherent irritant properties (33). It is unknown to what extent these pathogenic mechanisms impact on disease manifestation. Once again,

as the lack of a generally accepted classification system for hand eczema shows, the diagnostic criteria for skin irritancy can be used rather arbitrarily when combined diagnoses are assigned to patients in wet occupations with or without an irritant component (6, 20). As long as no biomarkers or tests exist for skin irritancy, it is of utmost importance to be consistent in the assignment of the diagnosis of combined allergic and irritant contact dermatitis (Table 4).

Conclusion

The statistically calculated expected number of patients with the diagnosis of combined allergic and irritant contact dermatitis in a retrospective cohort of 1000 consecutive patients indicates that this diagnosis should be assigned rarely.

Knowledge on genotype/phenotypes, may in the future, give clinicians new ways to guide their patients to opt out of occupations in which they are at high risk of developing combined allergic and irritant contact dermatitis. As long as no special biomarkers or routine tests for the diagnosis of irritant contact dermatitis exist, we suggest that the diagnosis should only be assigned if specific information exists qualifying the role of an irritant exposure in the dermatitis, and should not be based only on wet work criteria and the present criteria for irritant contact dermatitis.

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