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CONTACT DERMATITIS (BRANDON ADLER AND VINCENT DELEO, SECTION EDITORS)

Irritant Contact Dermatitis — a Review

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Abstract

Purpose of Review Irritant contact dermatitis is the most common form of contact dermatitis and the most common occupational skin disease. This review provides a comprehensive summary of the endogenous and exogenous factors that play a role in the pathogenesis of irritant contact dermatitis.

Recent Findings In conjunction with avoidance of irritants, barrier protection, and regular application of moisturizers, management now emphasizes the importance of primary prevention through educational initiatives in high-risk workplaces.

Summary The diagnosis of irritant contact dermatitis is often difficult, as there is no confirmatory test, and it is often a default diagnosis after allergic contact dermatitis has been excluded. Early recognition, prevention, and treatment are vital in management, especially in the occupational setting.

Keywords Irritant contact dermatitis · Skin irritation · Occupational · Hand · Allergy · Patch testing

Introduction

Irritant contact dermatitis (ICD) is an inflammatory cutaneous condition caused by skin barrier disruption, in combination with the activation of innate immune responses. ICD results from skin barrier damage from external agents or environmental factors. ICD commonly affects the hands and can affect people of all ages and sex. ICD is more prevalent than allergic contact dermatitis (ACD) [1] and is the most common presentation of occupational skin disease (OSD). At a tertiary referral occupational dermatology clinic in Australia, ICD was diagnosed in 71% of patients with OSD [2••]. However, in the general patch testing population, the most common diagnosis is ACD with a default diagnosis of an endogenous dermatitis, so ICD is less commonly diagnosed [3]. High-risk occupations for ICD include healthcare workers, food service workers, metal workers, hairdressers, and construction workers [4].

This article is part of the Topical Collection on *Contact Dermatitis*

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The purpose of this review is to provide a comprehensive update with regard to the pathogenesis, risk factors, clinical features, and management of ICD.

Contributing Factors in the Development of ICD

Both exogenous and endogenous factors play a vital role in the pathogenesis of ICD [5].

Exogenous

Skin Irritants

The most common skin irritant is wet work [6] followed by soaps, detergents, solvents, and oils [7]. Wet work has been defined as:

1. Exposure of skin to liquid for > 2 h per day
2. Use of occlusive gloves for > 2 h per day or change of gloves > 20 times per day
3. Frequent hand washing > 20 times per day or use of hand disinfectants > 20 times per day [8]

Exposure to wet work can occur both at work as well as at home. High-risk occupations involving wet work include cleaners, butchers, cooks, beauticians, and health care

workers [9•]. The only regulations regarding exposure to wet work are found in Germany, the Technical Standards for Hazardous Substances (TRGS) 401[10], a guideline for employers, providing information on occupational hazardous skin exposure and prevention of OSD.

Since the start of the COVID-19 pandemic, the use of soaps and alcohol-based hand sanitizers (ABHS) and the frequency of handwashing have increased significantly [11] resulting in a higher incidence of ICD [12, 13].

The potency of a chemical irritant and its ability to penetrate the skin are denoted by its properties including molecular size, ionization state, and fat solubility. Different irritants target different structures in the epidermis. For example, sodium lauryl sulfate targets lipid synthesis [14] whereas acetone targets the proliferation of basal keratinocytes [15].

Factors such as concentration, volume, and duration of irritant exposure will all contribute to an irritant's ability to penetrate the skin. Increasing the volume and duration of exposure will enhance the ability of an irritant to penetrate the skin [16]. Increasing intervals between exposures will usually reduce the chance of irritation. Recurrent irritant exposure may result in an additive effect, with repeated exposures initially inducing an increase, then a reduction in trans-epidermal water loss (TEWL) [17], indicating functional adaptation or skin hardening.

Physical, Mechanical, and Environmental Factors

The role of physical, mechanical, and environmental factors in the development of ICD is often ignored. Mechanical factors include occlusion, friction, pressure, and vibration. The use of gloves or clothing can create an occlusive, humid environment, which increases irritation caused by heat and sweating.

Environmental factors include heat, cold, humidity, and UV irradiation. Exposure of skin to heat often results in sweating. The retention of sweat can contribute to skin irritation, as sweat is more irritating than water [18]. Heat, especially in combination with occlusion, can precipitate ICD.

Exposure to low ambient humidity and cold temperatures are contributing factors to reduced water content in the stratum corneum (SC) and as a result increase the permeability of irritants in the skin. Cold temperatures have also been associated with reducing the plasticity of the horny layer with subsequent cracking of the SC; however, a study has shown that exposure to cold averted the development of ICD [19].

Endogenous

Age

Susceptibility of the skin to irritants decreases with age. It is postulated that differences in microcirculatory efficiency, percutaneous penetration, SC turnover time, and loss of corneocyte cohesion [20] associated with increasing age cause a slower and less intense response to irritants. This is reflected in the decrease of TEWL in aged skin [21].

Sex

ICD is more common in women [22], likely as a result of greater exposure to irritants rather than biological factors. A study from Denmark showed women had 78% higher odds of engaging in occupations involving wet work [9•]. It is not clear whether women have a greater susceptibility to irritants, given that experimental studies show no difference of irritant reactivity between sexes [21]. However, one study produced differing results [23] demonstrating an increased skin reactivity in males compared to females. Further studies are required to determine the difference in risk of developing ICD between sexes.

Race

There is a paucity of evidence to demonstrate a significant difference between black or Asian and Caucasian skin. Studies using bioengineering techniques showed no difference in irritant susceptibility between black and Caucasian skin [24] despite conflicting results from previous studies that relied on visual scoring [25]. A study showed Asian skin was significantly more susceptible to ICD when compared to Caucasian skin both in subjective and objective skin measurements [26].

Atopy

Atopy is a recognized risk factor for ICD involving the hands [27]. Mucosal atopy is less predictive of irritant reactivity, compared to prior atopic dermatitis (AD) [28]. Individuals with a history of AD are thought to have a higher risk for the development of ICD, relating to impairment of the epidermal barrier, higher TEWL, and increased skin permeability to allergens and irritants, compared to those with clinically normal skin [29].

Genetic Factors

Filaggrin is a protein which plays a role in skin barrier function and SC hydration. Filaggrin loss-of-function mutations are associated with increased expression of interleukin (IL)-1, a cytokine which is key to the initiation of the inflammatory response in ICD [30]. A study has shown an increased risk of the development of ICD in individuals with filaggrin loss-of-function mutations;

however, it was observed that the association was dependent on the presence of atopy [31]. Atopy, in combination with filaggrin loss-of-function mutation carrier status, has shown to contribute to the severity of ICD affecting the hands [32].

Single nucleotide polymorphisms (SNPs) within the major histocompatibility complex (MHC) class I, II, and III are significantly associated with skin response to irritants [33, 34]. MHC SNPs have been demonstrated to contribute to chemical irritancy thresholds, with different MHC variants being associated with different chemical irritants. At present, the exact mechanism is unknown.

A link has been recognized between a tumor necrosis factor (TNF)-α gene polymorphism and susceptibility to ICD. At the position P308 within the promoter region of the TNF-α gene, a G to A transition polymorphism has been detected. A study of genotypes showed an association between the A allele and a low irritant threshold [35], which has also been significantly linked to contact sensitization to allergens such as p-phenylenediamine (PPD) [36] and chromium [37]. Another G to A transition polymorphism at the position of P238 has been identified. A study found a potential protective effect of the A allele with carriers being less susceptible to developing ICD [38]. This has been speculated to result from increased transcriptional repression of TNF α [39, 40].

These advancements represent a novel potential approach in the detection of ICD susceptibility.

Pathogenesis

Previously, the pathogenesis of ICD was thought to be a non-immunological reaction; however, it is now recognized that the immune system plays a vital role in causing ICD [41].

Irritation occurs by either damaging epidermal cells [42], disruption of the epidermal barrier, or a combination of both [43]. Disruption of the epithelial barrier allows for increased permeability of irritants [44]. Keratinocytes act as "signal transducers" responsible for instigating cutaneous inflammation via the conversion of exogenous stimuli into the secretion of cytokines, adhesion molecules, and chemotactic factors [45]. Upon damage to the keratinocyte, upregulation of primary cytokines IL-1α, IL-1β, and TNF-α occurs [46] which triggers the proliferation of keratinocytes and formation of lipids [47] playing a role in restoring the epidermal barrier. Additional cytokines IL-6, IL-8, and GM-SCF are subsequently secreted, activating Langerhans cells, dermal dendritic cells, and endothelial cells [44] which further recruits inflammatory cells to the site of chemical trauma [48].

ICAM1, an adhesion molecule, is upregulated on endothelial cells and fibroblasts in the skin and results in the secretion of further chemokines including CXCL 8, CCL 20, and IFN gamma [49]. CCL21, a chemokine which enables naïve T lymphocyte migration, is upregulated in ICD [46, 50]. T lymphocytes recruited to irritated skin often express the CLA antigen [51], which plays an important role in transendothelial T lymphocyte migration.

Irritants can also trigger pattern recognition receptors such as toll-like receptors (TLRs) and NOD-like receptors, which result in activation of the innate immune response via inflammasome and NFκB pathways [44, 52].

There is growing evidence that oxidative stress with the formation of reactive oxygen species plays a role in the pathogenesis of ICD [53]. It has been postulated that targeting oxidative stress could be beneficial in the treatment of ICD, with clinical studies demonstrating the therapeutic benefits of antioxidants [54].

Clinical Types

Acute Irritant Contact Dermatitis

Acute ICD occurs when the skin is exposed to a potent irritant often in a single exposure, such as concentrated acids, strong alkalis, and solvents such acrylonitrile. In severe cases, this may present as burns, such as from kneeling in wet concrete.

The irritant reaction quickly reaches a peak and then begins to heal, usually described as a "decrescendo phenomenon" [55]. Symptoms reported include burning, stinging, and soreness of affected skin. The clinical signs of ICD are variable and include erythema, edema, bullae, and necrosis [56]. While ACD may present with similar clinical signs, it is characterized by a "crescendo phenomenon" where signs worsen, despite removal of the offending allergen [55].

Complete healing can take weeks in acute ICD, generally with a good prognosis [57].

Delayed Acute Irritant Contact Dermatitis

Delayed acute ICD represents the most common form of ICD. Chemicals such as benzalkonium chloride, anthralin, calcipotriol, and tretinoin may cause a delayed inflammatory response, not visible until 8–24 h after primary exposure [58]. This may lead to misdiagnosis as ACD. Clinical symptoms are similar to acute ICD with the skin becoming sensitive to touch and water [59].

Irritant Reaction

Irritant reaction is a subclinical type of ICD that typically affects individuals exposed to wet work. Clinical features are monomorphic, characterized by erythema, scaling, vesicles,

pustules, and erosions [59]. It often begins on fingers under occlusive jewelry such as rings and spreads to involve the hands and forearms.

This condition may spontaneously resolve with cessation of exposure, or can also progress to cumulative ICD [60].

Subjective/Sensorial Irritation

Subjective or sensorial irritation is characterized as sensory discomfort in the form of stinging, burning, or a sensation of itch, in the absence of clinical or histological evidence of skin irritation. Neural pathways are believed to be responsible [61]. Irritants identified include propylene glycol, hydroxy acids, ethanol, lactic acid, azelaic acids, benzoic acid, benzoyl peroxide, mequinol, and tretinoin.

Non-Erythematous Irritation

Non-erythematous ICD refers to early skin irritation without clinical signs of inflammation. Associated SC barrier changes can be demonstrated using assays that are usually available only in research settings [62]. Symptoms are comparable to subjective irritation. Prognosis is variable.

Cumulative (Chronic) ICD

Cumulative ICD is a result of multiple subthreshold insults to the skin, if the interval between skin exposures is too short to allow complete recovery of the skin barrier function [63]. It develops slowly and is linked to exposures to weak irritants [64].

Clinical features include erythema, vesicles, and dryness with progression to lichenification, hyperkeratosis, and chapping. Clinical features develop when the damage goes beyond the elicitation threshold. The threshold is dependent on the individual and may decrease as the disease progresses.

Given that exposure to weak irritants often occurs both at home and in the workplace, cumulative ICD may result from exposure to multiple irritants, rather than a single agent. The impact of combined multiple irritants produces an increased skin inflammatory response; however, the extent of interactive effect is unpredictable [65].

Frictional Dermatitis

Frictional dermatitis results from repeated frictional trauma, specifically shearing forces acting horizontally to the skin surface [66]. It is characterized by hyperkeratosis, acanthosis, and lichenification. Frictional ICD is recognized to contribute to ACD by enhancing percutaneous penetration of allergens [66].

Traumatic ICD

Traumatic ICD occurs after acute trauma to the skin such as burns, lacerations, or exposure to a potent irritant. The hands are the most commonly involved; however, there are reported cases of nail involvement [67]. Usually, there is delayed healing of the original trauma followed by the development of eczematous lesions [64]. It is usually a chronic condition and may be resistant to treatment.

Pustular and Acneiform Dermatitis

Exposure to oils, naphthalene, chlorinated aromatic hydrocarbons, and fluorinated compounds may result in pustular and acneiform dermatitis. Patients most affected are those with seborrheic dermatitis, prior acne vulgaris, and atopy. The prognosis is variable.

Asteatotic Irritant Dermatitis

Asteatotic irritant dermatitis, also referred to as "exsiccation eczematid," "winter eczema," and "eczema craquelé," is seen primarily during winter in cool climates. This variant is common amongst the elderly with dry skin on the lower legs, especially in low-humidity environments. Individuals report intense pruritus, dry skin, and scaling. Reduction in natural moisturizing factors and lipids in the SC is thought to contribute. Intense pruritus is usually relieved by the use of moisturizing creams, and topical corticosteroid ointments are helpful [68].

Airborne Dermatitis

Airborne ICD results from exposure to irritants such as fibers, floating dusts, solvents, and sprays [69] dispersed and carried in the air before coming into contact with exposed skin [64]. Most cases are reported in occupational settings [70].

Diagnosis

ICD is a diagnosis of exclusion, as there is no routine diagnostic test. The diagnosis is established from the history, clinical examination, and by excluding ACD with negative patch testing. A thorough history regarding occupational and domestic exposures is crucial, and relevant information includes the frequency, intensity, and duration of exposure to skin irritants, as well as the affected skin area(s) [44].

The pattern and distribution of dermatitis plays a key role in the diagnosis. ICD always starts at the site of skin contact with the irritant and generally does not spread. Common

sites include the hands, face, and perineal areas, particularly in infants and adults experiencing incontinence.

Patch testing is recommended to exclude the differential diagnosis of ACD, which may be clinically indistinguishable from ICD. Even if the results are negative, patch testing has been shown to have a positive impact on quality of life [71].

Bioengineering techniques, such as the measurement of TEWL, provide a non-invasive method to measure skin irritation in ICD; however, these are not always available in a clinical setting.

The role of skin biopsy remains limited in the diagnosis of ICD, given that histopathological changes vary between irritants and relates to their mode of action and concentration [72]. Histological findings in chronic ICD are generally similar to those of ACD. Reflectance-mode confocal microscopy (RCM) is a non-invasive novel technique which can be used to differentiate between acute ICD and ACD in experimental settings, with superficial epidermal changes (SC disruption, parakeratosis, and separation of individual corneocytes) being more prominent in ICD compared to ACD [73, 74]. RCM is postulated to be more sensitive and specific than clinical examination during patch testing and could potentially play a role in distinguishing between doubtful-positive and negative reactions [75]. RCM allows repeated observation of the affected area in real time, which is non-invasive compared to conventional histology [76].

Prevention

Approaches to preventing exposure to irritants in the workplace involve standard occupational hygiene principles including elimination and/or substitution of the irritant, isolation, and engineering controls including changing the way a job is performed, administrative controls, and finally use of personal protective equipment (PPE) [77].

Recent studies have highlighted the importance of pre-employment screening tools in the workplace in early identification of hand dermatitis [78].

The use of PPE is recommended in the prevention of ICD. The choice of PPE is guided by the nature of the irritants, the areas of skin exposed, the chemical and physical properties of PPE, and its functionality in relation to the occupation [79].

Gloves are a frequently used form of PPE, given that ICD usually affects the hands. Selection of appropriate gloves for the management of ICD may be challenging, given that the protective capabilities of gloves are dependent on many variables.

Gloves should be selected based on the specific task and associated chemical exposures. The nature of the irritant as well as glove permeation time will determine the necessary type of glove material [80]. For example, neoprene gloves have been shown to be the most protective against acrylate monomers compared with polythene polymer gloves [81]. Occasionally, components of protective gloves can cause sensitization and ACD; common culprits include thiurams and carbamates found in both latex and nitrile gloves, but are absent from those made of polyvinyl chloride [82].

Glove thickness plays a major role in chemical permeation. However, thin gloves provide greater user comfort and dexterity than thicker gloves made from the same material [83].

Even when a suitable glove has been chosen, if the user does not don or remove the glove appropriately, skin contamination can occur. Incorrect glove sizing can increase the rate of glove perforation [84]. It is important that gloves are changed regularly, as sweating may exacerbate existing dermatitis [85]. Additionally, there is evidence that occlusion from gloves may impair the function of the skin barrier [86].

Training in glove choice and use has been shown to reduce user error and allergen exposure [87, 88]; however, studies have shown that workplace glove education remains limited [89, 90].

Given that half of the cases of occupational contact dermatitis (OCD) have been observed to appear within the first 2 years of employment [91], there is a role for educational strategies to promote awareness of potential irritants, appropriate use of PPE, and recognition of the early signs of OCD, specifically ICD. Interdigital dermatitis, also referred to as the "sentinel" sign, is regarded as an early stage of hand ICD in occupations involving wet work [92]. The impact of work-related educational programs has been shown to be effective in Danish healthcare workers [93], student nurses [94], and hairdressers [95].

A soap-free cleanser is preferable, as synthetic detergents are less irritating to the skin because of the neutral or slightly acidic pH [96]. The relatively high-free fatty acid content of soap free cleansers also provides a moisturizing effect, preventing hand irritation and dryness. The use of ABHS including moisturizers avoiding common allergens is recommended as an alternative to detergents [97].

Barrier creams (BCs) are designed to prevent penetration of irritants into the skin. They are thought to play a role in the prevention of ICD but are only recommended for low grade irritants [98]. A recent Cochrane review found that use of barrier creams alone may have a slight protective effect, but the evidence was deemed low quality and not clinically significant [99••]. Application methods can impact the efficacy of barrier creams, with studies highlighting that BCs are often poorly applied during real-world use, especially on the dorsa of the hands and at significantly lower doses than required to prevent irritation [100]. Inappropriate application has been shown to exacerbate some skin conditions [101]. Nevertheless, BC can raise awareness of the possibility of skin problems in the workplace.

Inflammasome-targeted therapies such as topical disulfiram have been shown to be effective in inhibiting ICD in a recent study on human subjects [102]. This is thought to be a result of the reduction in the inflammatory cytokine IL-18. This advancement provides a novel approach in the prevention of ICD.

Management

The primary treatment in ICD is avoidance, skin protection from the offending irritant(s) both in the workplace and at home [103], and use of topical therapy, particularly moisturizing creams.

Moisturizers are commonly used to improve dry skin symptoms and maintain healthy skin [104]. There is increasing evidence of their role in the treatment of ICD by preventing the absorption of exogenous substances and improving skin barrier recovery [105]. It is thought that using moisturizers increases skin hydration and that their lipid components modify endogenous epidermal lipids, with high lipid content moisturizers significantly preventing ICD when compared to formulations with lower lipid content [104]. Patients should be advised to apply moisturizers frequently, particularly before and after shifts, and after handwashing [106]. Evidence has also shown the protective role that moisturizers play in the long and short term, in the primary prevention of occupational ICD [99••, 107].

Strontium salts have been shown to be effective in treating sensory irritation and are thought to act by selectively blocking the activation of cutaneous type C nociceptors [108]. However, this treatment is not commonly used worldwide.

Cool compresses are a primary treatment of acute ICD by providing an environment which reduces the inflammation and surface temperature changes associated with acute ICD [109, 110].

Complications of ICD include bacterial superinfections. These are usually treated aggressively with antibiotics to prevent the development of cellulitis.

Although histamine is not involved in the mechanism of ICD, in clinical practice, oral antihistamines are often prescribed for symptomatic relief. Studies on mice have shown the potential role of topical antihistamines in ICD by reducing inflammation and enhancing barrier function [111]. However, to date, there have been no randomized clinical trials demonstrating the efficacy of antihistamines in ICD [111].

Despite the frequent use of topical corticosteroids in ICD, their use remains controversial. In humans, studies of clinical efficacy are inconsistent [112] with some suggesting that they may reduce barrier function associated with inhibition of lipid synthesis in the epidermis [113]. There may be a role for topical corticosteroids in chronic hyperkeratotic irritant dermatitis [56], but prolonged use can result in epidermal atrophy and therefore increase irritant sensitivity. However, systemic corticosteroids may be required during severe acute phases of ICD [114].

The Osnabrueck tertiary intervention program (TIP) is a multidisciplinary approach intended to treat severe recalcitrant OSD, comprising a 3-week inpatient phase followed by a 3 week no-exposure outpatient phase. Therapy aims to be free of corticosteroids in order to promote long-term stabilization of the epidermal barrier. TIP intervention has been shown to significantly reduce the use of corticosteroids [115, 116, 117••]. Management also includes intensive patient education, health-psychological intervention, and specialized employment consultants [118]. Follow-up studies have shown a significant reduction in hand eczema severity and days of absence from work as well as improvement in quality of life both in short-term [115] and long-term follow up [116, 117••].

Topical calcineurin inhibitors (TCIs) are topical immunomodulators that provide a safe alternative to corticosteroids. An association of topical TCIs with skin cancer has been suggested, but there is no strong evidence [119], while there may be an association with risk of lymphoma [120]. TCIs have been shown to be favorable in the treatment of ICD [121, 122]. Other systemic treatments include alitretinoin, which has been shown to be an effective treatment in study of patients with chronic hand eczema, 43.2% of whom were diagnosed with ICD [123].

Oral immunomodulators may be required in the treatment of chronic ICD if other first- or second-line treatments fail. Cyclosporine is reported to be beneficial in the treatment of chronic hand eczema [114] but is used with caution given its associated side effects.

Limited evidence has highlighted the use of dupilumab, a monoclonal antibody treatment approved for the treatment of atopic dermatitis, to be effective in the treatment of chronic recalcitrant hyperkeratotic ICD [124] and non-atopic hyperkeratotic hand eczema [125]. Further studies are required to determine the use of dupilumab as a potential therapeutic agent in ICD.

Phototherapy has proven to be beneficial in the treatment of cumulative ICD, where repeated low levels of UV exposure upregulate skin barrier function by reducing epidermal proliferation [126]. Grenz–ray therapy is an alternative which may induce an extended response by suppressing Langerhans cells [127, 128].

Prognosis

Severe ICD is associated with a poor prognosis despite advancements in prevention and treatment strategies. A worse prognosis is linked to history of atopy, female sex, and delayed diagnosis [44]. Prognosis can be improved with early detection, patch testing to clarify the diagnosis, and exclude ACD and educational interventions to increase knowledge of ICD in affected individuals [129].

Conclusion

ICD is a complex disease influenced by endogenous and exogenous factors. ICD remains a diagnosis of exclusion, and currently, there is no diagnostic test available. For many clinicians, the diagnosis may be difficult, especially if patch testing is not available. Delays in diagnosing ICD are associated with a poorer prognosis. Advancements into RCM as a diagnostic approach appear to be promising. The mainstay of treatment in ICD remains avoidance of skin irritants and the use of PPE, with moisturizers to maintain skin barrier function. In cases of occupationally acquired ICD, the role of health promotion and preventative strategies has been shown to be beneficial, but are often poorly implemented in workplaces. Further studies are required to more fully evaluate predisposing factors, as well as informing clinicians of therapeutic approaches to better manage ICD.

Abbreviations ACD: Allergic contact dermatitis; ICD: Irritant contact dermatitis; CLA: Cutaneous lymphocyte association; OSD: Occupational skin disease; PPE: Personal protective equipment; SC: Stratum corneum; TEWL: Trans epidermal water loss; TNF: Tumor necrosis factor

Compliance with Ethical Standards

Conflict of Interest Kajal Patel and Rosemary Nixon declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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