

Superantigens: a brief review with special emphasis on dermatologic diseases

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A. Brief review of superantigens

1. General considerations and history

Superantigens are microbial or viral toxins that comprise a class of disease-associated, immunostimulatory molecules and act as V β -restricted extremely potent polyclonal T cell mitogens. They bind major histocompatibility complex (MHC) class-II molecules without any prior processing and stimulate large number of T cells (up to 20% of all T cells) on the basis of epitope specified by this receptor [1, 2, 3]. These properties are attributable to their unique ability to cross-link MHC class II and the T cell receptor (TCR), forming a trimolecular complex [1, 2]. Here we present a brief overview of superantigens with special emphasis on their role in dermatological diseases.

In 1978 Todd et al. characterized toxic shock syndrome (TSS) as a discrete clinical entity and established that it is a manifestation of staphylococcal infection [4]. Subsequently in 1981, Schlievert et al. and Bergdoll et al. [5] isolated pyrogenic exotoxin C (PEC) and staphylococcal enterotoxin F (SEF), respectively. In 1989 this fundamentally new class of antigens was recognized and termed as "superantigen" by Kappler and Marrack [6, 7].

2. Classification

The superantigens can be broadly classified into following families:

- i. Endogenous superantigens: These superantigens are encoded by various viruses integrated into the genome. Examples are superantigens produced by mouse mammary tumor virus (MMTV) and Epstein-Barr virus (EBV) associated superantigen [6, 8-11].
- ii. Exogenous superantigens: These include the exotoxins secreted by microorganisms. Examples are staphylococcal enterotoxins (A, B, C1 to C3, etc.), streptococcal pyrogenic exotoxins (A1 to A4, C, etc) and others (see Table 1) [7, 12-18].
- iii. B-cell superantigens: Those superantigens which stimulate predominantly B cells. Examples include staphylococcal protein A and protein Fv [19, 20, 21].

3. Structure

Superantigens are globular proteins synthesized as 25-30kDa precursors and secreted as 22-29kDa proteins. They are resistant to proteases and heat denaturation and are able to adsorb by the epithelium as immunologically intact proteins [1]. The macromolecular structure of superantigens can be studied by X-Ray crystallography and solution nuclear magnetic resonance spectroscopy [22]. They have a common two-domain architecture (amino and carboxy terminal domains) with a long solvent accessible α -helix (part of the carboxy terminal domain) spanning the centre of the molecule [1].

The amino terminal domain consists of concave β -barrel with α -helix at one end. This domain

resembles the 'oligosaccharide-/oligonucleotide-binding fold' (OB-fold) present in other protein families. In these proteins, the OB-fold is involved in DNA binding and carbohydrate recognition, respectively, but no such functions have yet been attributed to superantigens. Other features of the amino-terminal domain include the presence of several hydrophobic residues in solvent-exposed regions of the molecule, and a disulphide bridge. The residues between the two cysteines in the amino acid sequence form a highly mobile loop region [1].

The carboxy-terminal domain consists of four stranded β -sheet flanked by a long central α -helix and has some structural features of β -grasp motif present in other proteins like ubiquitin, immunoglobulin-binding domains etc. In addition, the amino-terminal tail (~15-20 residues in length) is packed against the β -grasp motif and it is considered part of the carboxy-terminal domain [1].

Most of the superantigens, except SEB, TSST-1 and SSA, possess either one or two zinc-binding sites, but the location varies in different superantigens. The zinc-binding sites seem to have a direct effect on the recognition of superantigens by MHC-class II molecules [1]. The three-dimensional structures of various superantigens are available on the internet [23].

4. Bioactivity

Superantigens, like conventional antigens/haptens, activate antigen-presenting dendritic cells by producing increased expression of HLA-DR antigen and co-stimulatory molecules (CD54, CD83 and CD86) and the production of tumor necrosis factor (TNF) - α [24, 25]. This augmentation by superantigens can be suppressed by both corticosteroids and cyclosporine, while conventional antigen/hapten-induced augmentation is resistant to suppression by cyclosporine [25].

Figure 1

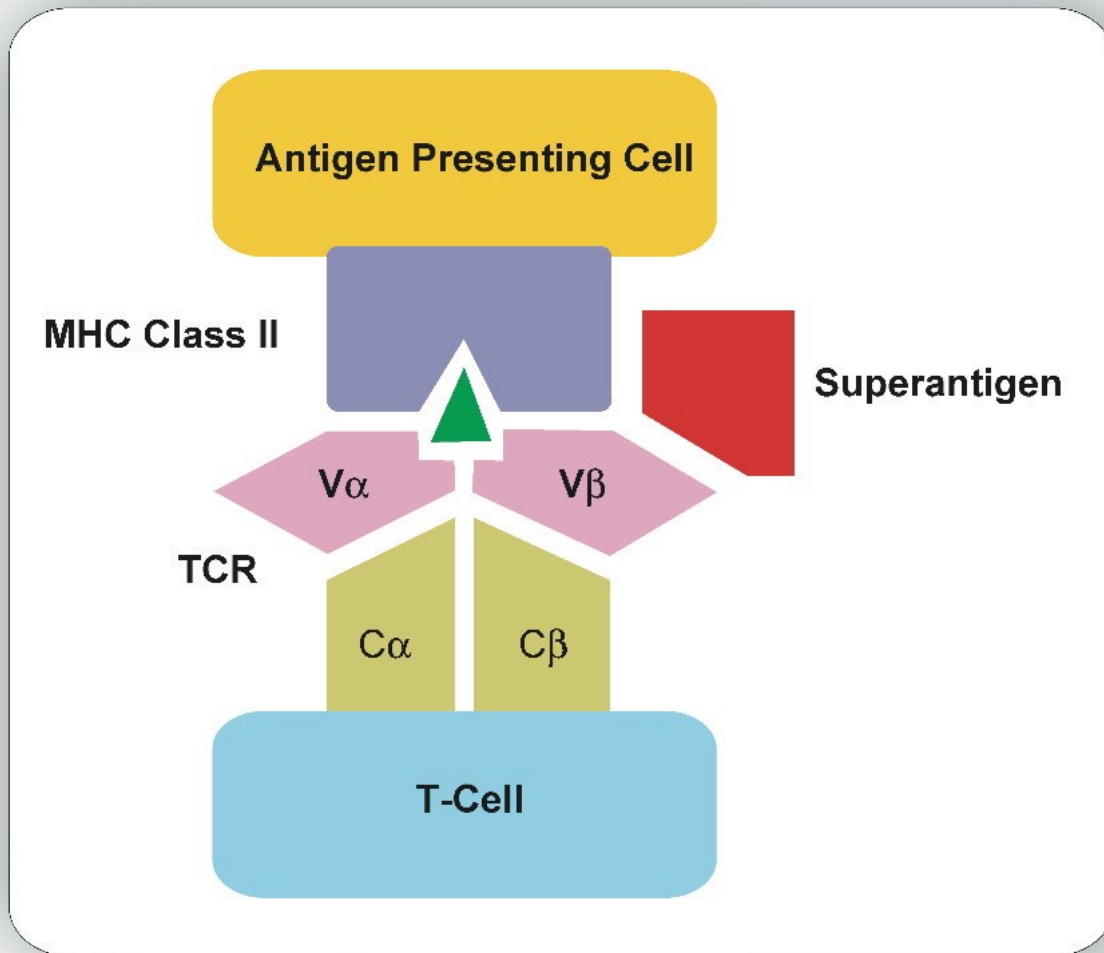


Figure 1. Schematic diagram showing the binding of superantigen (red) and conventional antigen (green) with major histocompatibility complex (MHC class II) and T cell receptor (TCR) molecules.

Superantigens are active at very low concentration i.e., 10mol/L [26]. Superantigen's bioactivity depends on its ability to bind both the MHC class II and TCR. Once secreted, superantigens require no processing in order to interact with the antigen-presenting cell. They interact with MHC class II molecules outside the antigen binding groove, and yet are still able to elicit a productive interaction with T cells (Fig. 1). However, differences in amino acid sequences dictate that each superantigen has an affinity for specific MHC class-II alleles [1, 6].

The MHC class-II superantigen complex is readily recognized by large families of T cells, limited only by the TCR $V\beta$ subunit that each family expresses. Most superantigens will be recognized by at least three to five types of TCR families. After binding with T cell receptor superantigen activates large number of resting T cells, as many as 20 percent of total T cells [27]. This is followed by proliferation of T cells and their activation-induced clonal deletion. Both in vivo and in vitro superantigen-induced T cells lead to production of elevated amounts of inflammatory cytokines such as $\text{TNF-}\alpha$ and $\text{-}\beta$, interleukin (IL)-2, and $\text{INF-}\gamma$ [1, 27]. Differences between superantigens and conventional antigens are presented in see Table 2) [6, 27-30].

5. Association of superantigens with diseases

Association of superantigens with different diseases is summarized in see Table 3 [28, 30-99].

B. Importance of superantigens in dermatology

1. Staphylococcal toxic shock syndrome

Toxic shock syndrome (TSS) is a multi-organ systemic illness due to exotoxin-producing strains of *S. aureus*. It is characterized by a generalized erythematous eruption and high fever. Additional elements of syndrome include hypotension, functional abnormalities in at least three organ systems, and desquamation following the scarlatiniform eruption [33].

Toxic Shock Syndrome occurs in two forms: menstrual and non-menstrual. Toxic Shock Syndrome that occurs during menstruation is associated with use of super-absorbent tampons, which cause cervicovaginal ulcerations and creates a portal for toxin absorption. Super-absorbent tampons also allow increased oxygen tension which results in increased amount of toxin production [34]. Non-menstrual TSS occurs in association with staphylococcal infections (skin, soft tissues, bone, and lung) in children, men, and non-menstruating women [33]. Recurrence usually occurs in menstrual TSS, which requires two factors, persistent colonization with toxin producing *S. aureus* and persistent absence of toxin neutralizing antibodies [34]. Toxin produced by menstrual-TSS associated strains of *S. aureus* is TSST-1. *S. aureus* strains of non-menstrual TSS produce TSST-1, SEB, SEC, and both TSST-1 and SEC1 in 48 percent, 26 percent, 7 percent and 19 percent of cases, respectively [35].

Superantigenic stimulation produced by these toxins lead to production of cytokines like IL-1 and TNF- α . Sudden increase in TNF- α is accompanied by changes in endothelial and vascular smooth muscle changes, which manifests as hypotension, shock, and features of sepsis [9, 27].

2. Staphylococcal scalded skin syndrome

It is a generalized exanthematous disorder with cutaneous tenderness, widespread blistering and superficial denudation. Strains of *S. aureus* that cause staphylococcal scalded skin syndrome (SSSS) usually belong to group II phage types 71 and 55, and sometimes to phage groups I and V [33]. The staphylococcal exfoliative toxins A and B (ETA and ETB), by their superantigenic property, act as trypsin-like serine protease [36] or act as lipase and activate other proteases [37]. They also bind directly to the desmosomal cadherin desmoglein I (DsgI), which results in disruption of desmosomes in the granular layer of epidermis, leading to interdesmosomal splitting, characteristic blistering and denudation of skin [36, 38]. Other clinical manifestations of SSSS are not explained by exfoliative toxins (ETs), but are probably caused by δ hemolysin secreted by *S. aureus*, a cytolytic toxin that has detergent like effect on cell membranes [39].

3. Staphylococcal scarlatiniform eruption

It is considered a milder variant of SSSS. Staphylococci belonging to phage group II are responsible. Strains causing this eruption produce staphylococcal enterotoxin (SEs) similar to the toxins responsible for TSS [33].

4. Guttate psoriasis and psoriasis vulgaris

Psoriasis is a common, chronic, inflammatory and proliferative skin disease, in which both genetic and environmental factors play crucial roles. Newer concepts suggest that it is a Th-1-mediated disease. Evidence shows that T cells in psoriasis are triggered by conventional antigens and

superantigens. It is suggested that although the process is initiated by bacterial superantigens, molecular mimicry between the bacterial antigens and keratin 17 leads to activation of autoreactive T cells and persistence of disease [40].

Acute guttate psoriasis is preceded or is concurrent with group-A streptococcal infection, particularly of throat [41, 42, 43] and is associated with rise in serum antistreptococcal titres [44]. As a result of superantigen activation, there is enhanced expression of V β 2 cells in acute skin lesions of patients with guttate psoriasis. It was found that there was selective expansion of V β 2+ cells in both the CD4+ and CD8+ infiltrating T cells in the dermis and epidermis of guttate psoriasis. Superantigens involved in the activation of V β 2+ T cells activation in guttate psoriasis were analyzed in the isolates of group A streptococcus by M typing and secretion of pyrogenic exotoxins A, B, and C [41]. Results showed that in most patients there is no consistent M protein type. Some isolates secreted SPEA, others SPEB, which could explain the expansion of V β 8 seen in some patients. All streptococci secrete SPEC, a superantigen known to stimulate marked expansion of V β 2+ T cells, therefore it appears to play important role in the pathogenesis of this disease [41].

To explain eruption of lesion of guttate psoriasis following streptococcal infection of throat, it has been postulated that after pharyngitis, skin-seeking T cells are induced in the lymph nodes draining the pharynx. After activation, these T cells then home to the skin via (CLA)/E-selectin interaction and may be further locally activated by a skin-specific antigen that is recognized by V β 2+T cells. Recent evidence further supports the hypothesis that SPEC and other bacterial superantigens potentially induce the expression of skin-homing receptor cutaneous lymphocyte-associated antigen (CLA) on T lymphocytes, in an IL-12 dependent manner [41]. Patients with guttate psoriasis frequently improve with systemic antibiotic therapy [45].

A recent prospective study has confirmed anecdotal and retrospective reports that streptococcal throat infection can cause exacerbation of chronic plaque psoriasis [46].

5. Kawasaki syndrome

Kawasaki syndrome (KS) is an acute multisystem vasculitis that primarily affects infants and young children. It is widely agreed that KS is caused by an infectious agent because of the acute, self-limited nature of this disease, seasonal incidence, geographic clustering of outbreaks, and the unique susceptibility of young children. Furthermore, fever and other clinical findings in acute KS overlap with bacterial toxin mediated disease such as toxic shock syndrome (TSS) or scarlet fever. Initial few reports provided inconclusive evidence about V β 2 expansion in acute KS [47, 48, 49].

One study done on 19 children with KS, in which TCR V β gene usage was assessed, found that there was marked expansion of V β 2 and, to a lesser extent, V β 8 in patients with acute KS. During convalescence phase of KS, their percentages reached normal level [50]. Yamashiro et al. studied 12 patients and observed the selective expansion of V β 2-positive cells in the small intestinal mucosa in acute phase of KS. This suggests that gastrointestinal mucosa may be the primary site of entry of superantigens, produced locally by the bacteria colonizing the small intestine [51]. Potential bacterial superantigens involved in the pathogenesis were studied by Leung et al. in a blinded study [52]; they analyzed cultures of 16 patients in acute phase of KS. Superantigen producing bacteria were found in 13 of 16 patients with acute KS, but only 1 of 15 control patients ($p < 0001$). Of 13 toxins-positive cultures from patients with KS, 11 were TSST-1 secreting *S. aureus*, and 2 were streptococci, producing streptococcal pyrogenic exotoxin B (SPEB) and streptococcal pyrogenic exotoxin C (SPEC). TSST-1 and SPEC are known to possess V β 2 stimulatory activity, whereas SPEC has both V β 2 and V β 8 stimulatory activity. 12 of 13 culture-positive patients had toxin-producing *S. aureus* isolated from the pharyngeal or rectal cultures, again suggesting gastrointestinal tract as the primary site of entry. A few new trials also suggest role of TSST-1-

producing *S. aureus* and SPEC-producing streptococci in acute KS [52, 54]. Furthermore, there are three case reports of occurrence of psoriasis following KS suggesting the role of superantigens in KS [55, 56, 57].

6. Atopic dermatitis

Atopic dermatitis (AD) is a genetically determined, chronically relapsing, inflammatory skin disease that has a complex immunopathogenesis involving both immediate hypersensitivity and cellular responses. Superantigens fulfill Koch's postulates in AD as application of superantigen SEB to the skin induces skin erythema and induration accompanied by the infiltration of T cells that are selectively expanded in response to SEB [58, 59, 60].

Although the pathogenic role of superantigens may not be of primary importance, superantigens appear to be one of the important triggering factors that contribute to the cutaneous inflammation in AD [61]. *Staphylococcus aureus* is found on more than 90 percent of AD skin lesions; only 5 percent of normal individuals harbor this organism [62]. The density of *S. aureus* on inflamed AD lesions without clinical superinfection can reach up to 107 colony forming units per cm². *S. aureus* exacerbate or maintain skin inflammation in AD through superantigens that stimulate marked activation of T cells and macrophages. The skin lesions of over half of AD patients contain *S. aureus* that secretes superantigens such as SEA, SEB and TSST-1 [63, 64].

Scratching disrupts the skin barrier in AD and leads to exposure of extracellular matrix molecules (fibronectin, collagen) which act as adhesins for *S. aureus*. IL-4 also enhances binding of *S. aureus* to skin by stimulating the synthesis of fibronectin [65]. In another study, bacterial binding was found to be more at the sites with Th-2 mediated inflammation [66]. Studies of peripheral blood skin-homing CLA⁺T cells from these patients, as well as T cells in their skin lesions, reveal that they had undergone a T cell receptor (TCR) V β expansion consistent with superantigenic stimulation [68, 69]. Clinical evidence for the role of *S. aureus* in AD includes demonstration of greater reduction in severity of lesions on treatment with combination of antistaphylococcal antibiotic and topical corticosteroid compared to topical corticosteroid alone [67].

Superantigens also induce specific IgE in AD patients and also cause mast cell degranulation in vivo, which promotes itch-scratch cycle critical to the evolution of skin rashes in AD patients. Correlation exists between presence of IgE antibodies against superantigens and severity of AD [61].

7. Cutaneous T-cell lymphoma

Cutaneous T-cell lymphoma (CTCL) is a malignancy of skin-homing T cells that are best delineated from other T cells by a unique cell surface receptor called CLA, a glycoprotein that is expressed on memory T cells that have the ability to home to skin by binding to E-selectin present on endothelial cells. Association of *S. aureus* with CTCL has been shown in a study in which 75 percent of patients showed positive staphylococcus culture from blood or skin, with half of these cultures positive for *S. aureus* carrying enterotoxin genes, such as TSST-1. The patients with positive blood cultures had Sezary syndrome or progressive plaque and tumor stage mycosis fungoides but only rarely had monoclonal expansion of a specific V β gene. This study suggests that *S. aureus* superantigen enterotoxin could provide or potentiate lymphocytic infiltration and chronic antigenic stimulation leading to clonal expansion in CTCL [72]. Other studies have also shown dominance of single V β family in the polyclonally expanded dermal T cell population [73].

Superantigenic stimulation of T cells is selective for cell bearing particular β chain variable (V β) gene segments of the T cell receptor (TCR). In humans, staphylococcal exfoliating toxin (ExT) and

toxic shock syndrome toxin-1 (TSST-1) are known to stimulate V β -2 bearing cells; IL-1 can also act as a cofactor for stimulation of CTCL cells in combination with ExT [74]. Further studies proved the role of superantigens in leukemic phase of CTCL, by using antibodies directed against the β -chain of the T cell receptor (anti-V β antibodies), with increased V β 5.1 usage in CTCL than V β 2 usage [75]. Cutaneous colonization by *S. aureus* also influences the disease activity of CTCL, possibly by activation of Sezary cells by bacterial superantigenic exoproteins [76].

8. Acute juvenile pityriasis rubra pilaris

Acute juvenile pityriasis rubra pilaris is a form of pityriasis rubra pilaris (PRP) with particular clinical characteristics and course. It is usually preceded by an infectious condition and has similarities with other disorders mediated by superantigens. It has been postulated that streptococcal superantigen may have a role in the development of this disease. However, the exact nature and role of superantigen is not known [70, 71].

C. I.C. Drugs and therapies for superantigen-mediated diseases

1. Drugs currently available

i. Glatiramer acetate

Glatiramer acetate is a synthetic co-polymer of four amino acids based on the composition of myelin basic protein. It causes a significant reduction of proliferation of peripheral blood mononuclear cells (PBMC) as well as IFN- γ and TNF- α secretion. But these changes were observed in vitro, at concentration 200 microgram/ml, which is difficult to achieve physiologically [100]. Various double-blind, placebo-controlled trials have established its efficacy in relapsing-remitting multiple sclerosis and it is considered as one of the drugs of first-line choice [101].

ii. Polyclonal human intravenous immunoglobulins (IVIG)

The efficacy and safety of high dose intravenous polyspecific immunoglobulins G (IVIG) has been evaluated in multicentric, randomized, double-blind, placebo-controlled trial as an adjunctive therapy in streptococcal toxic shock syndrome as it neutralizes superantigen toxins [102]. Study in mice has shown that the IVIG preparation neutralized superantigenicity of *S. pyogenes* in vitro and enhances bacterial killing in a whole blood assay. When given to mice at the time of *S. pyogenes* infection, IVIG neutralizes circulating superantigens and reduced systemic inflammatory response. In delayed treatment settings, IVIG did not confer additional therapeutic benefit, in terms of reduction of inflammatory response, bacterial clearance or survival [103]. Different preparations of IVIG vary in their efficacy to neutralize the streptococcal superantigens, therefore there is need to optimize the type and dose of intravenous immunoglobulins used in adjunctive therapy for severe streptococcal diseases [104].

iii. Doxycycline

Pro-inflammatory cytokines mediate the toxic effect of superantigenic staphylococcal exotoxins (SE). Doxycycline inhibits SE-stimulated T cell proliferation and production of cytokines and chemokines by human peripheral blood mononuclear cells. This may explain the anti-inflammatory effects of doxycycline and its role in mitigating the pathogenic effects of SE [105].

iv. Anisodamine

Raceanisodamine hydrochloride is the active ingredient of a Chinese herbal extract that possesses

the chemical structure of tropane alkaloids. It has inhibitory effect on the production of TNF- α , IL- β , IL-8 from peripheral blood monocytes stimulated with shiga toxin (Stx). Shiga toxin is the major toxin responsible for hemolytic-uremic syndrome (HUS) caused by enterohemorrhagic *E. coli*. Anisodamine prolongs the survival of mice injected with Stx. Study has also shown the inhibitory effect of anisodamine on activation of T cells by TSST-1 and on the release of pro-inflammatory and anti-inflammatory cytokines from TSST-1-stimulated human peripheral mononuclear cells (PBMC) [106]. It also interferes with V β + T cell proliferation following injection of TSST-1, has protective effect on lethality of TSST-1 in mice, and has beneficial effects against various infections by gram-negative bacteria. This vasoactive drug has been used to treat acute disseminated intravascular coagulation in patients with bacteremic shock [106].

2. Experimental treatments

i. Pirfenadone

In vitro experiments with human peripheral blood lymphocytes revealed that pirfenidone reduced SEB-induced cytokine levels by 50-80 percent and inhibited about 95 percent of SEB-induced T cell proliferation [107]. Further study was conducted in BALB/c mice by exposing the mice with SEB, either systemically or by aerosol, and subsequently with a sublethal dose of lipopolysaccharide. In these experiments, pirfenidone given 2 to 4.5 hours after SEB resulted in 80 to 100 percent survival versus only 0 to 10 percent survival among untreated control animals. It also inhibited production of TNF- α from macrophages incubated with endotoxin and protects mice against endotoxin shock [107].

ii. Ketamine isomers

In human whole blood in vitro studies it has been shown that ketamine isomers significantly suppressed SEB-induced TNF- α production at concentrations exceeding 50 micromole [108]. Ketamine isomers at concentrations exceeding 100 micromole also significantly suppressed SEB-induced IL-6 production and at concentrations exceeding 500 micromole significantly suppressed SEB-induced IL-8 production. There is no significant differences between the effects of S(+)-ketamine and R(-)-ketamine forms [108].

iii. Triptolide

This is an oxygenated diterpene derived from a Chinese medicinal herb *Tripterygium wilfordii*. Triptolide inhibits SE-stimulated T cell proliferation by 98 percent and expression of IL-1 β IL-6, TNF- α , INF- γ , monocyte chemotactic proteins (MIP)-1 α , MIP-1 β by human peripheral blood mononuclear cells (PBMC) [109]. It also mitigated the effect of lipopolysaccharides in dose-dependent manner.

iv. Immunoglobulin Y

Passive transfer of antibody generated in chickens (IgY) against the staphylococcal enterotoxin-B (SEB) suppressed cytokine responses and was protective in mice [110]. All rhesus monkeys treated with the IgY specific for SEB upto 4 hours after challenge survived lethal SEB aerosol exposure. These results suggest the protective role of SEB specific antibodies in non-human primates [110].

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