Review Article

Dermatological adverse drug reactions due to systemic medications – a review of literature

A.K. Dubey*, S. Prabhu[†], PR Shankar*, P. Subish[‡*], M.M. Prabhu[!], P Mishra[‡*]

* Department of Pharmacology, [†] Department of Dermatology, **!** Department of Medicine, Manipal Teaching Hospital / Manipal College of Medical Sciences, Pokhara, Nepal. [‡] Department of Hospital and Clinical Pharmacy, Manipal Teaching Hospital, Pokhara, Nepal.

Abstract

Cutaneous adverse drug reactions (ADRs) affect 2-3% of hospitalized patients. These reactions can arise as a result of immunologic or non-immunologic mechanisms. Extremes of age, female sex, previous history of ADRs and environmental factors are the major risk factors. The severity of the cutaneous ADRs may vary from a mild itching to a life threatening Stevens-Johnson syndrome (SJS). In general, most are usually mild and respond to topical treatment. Different skin diseases and cutaneous manifestation of systemic diseases should be ruled out before diagnosing a cutaneous ADR. In order to establish the causal relationship between the offending drug and the reaction, causality assessment should be carried out. The Naranjo algorithm is widely used to determine the causality of an ADR. The cessation of the offending agent, along with the use of systemic and topical steroids, antipruritic agents and oral antihistamines may be helpful in the management. Patients with extensive skin involvement should be cared for as burns patients. High risk patients should be counseled regarding the possibility of developing a cutaneous ADR during the course of treatment and the strategies to be followed upon occurrence of a cutaneous ADR.

Key words

Cutaneous adverse drug reactions, causality assessment, Naranjo algorithm, South Asia

Introduction

Drugs can be remarkably beneficial, lengthen life and improve its quality by reducing symptoms and improving well-being. However, all drugs have adverse effects and carry the potential for causing injury, even if used properly. Proper data about the adverse effects of drugs helps physicians to use drugs balancing the benefits and hazards. An adverse drug reaction (ADR) has been defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product."[1] The skin and the mucosa are the commonest sites for initial presentation of many ADRs. Although the rate of acute severe adverse cutaneous reactions to medication is low, these reactions can affect anyone who takes medicines and can result in death or disability.[2]

Cutaneous ADRs affect 2-3% of hospitalized patients.[3] Fortunately, most cutaneous adverse reactions are not severe and few are fatal.[2,3]

Address for correspondence
Dr.P. Ravi Shankar, Assistant Professor,
Department of Pharmacology,
Manipal College of Medical Sciences,
PO Box No: 155,
Deep Heights, Pokhara, Nepal.
Phone: 00977-61-523600 Fax: 00977-61-522160.
E mail: pathiyilravi@gmail.com

Cutaneous or allergic reactions to drugs are responsible for approximately three percent of all disabling injuries during hospitalization.[4] Since most cutaneous ADRs are usually mild and respond to topical drugs, they are usually ignored. In addition to their human costs, ADRs are expensive to the health-care system. Two studies conducted independently arrived at estimates of about $2000 per event. Preventable events were even more costly at approximately $4500 per event.[5,6] In this article, the authors make an attempt to explain the nature of cutaneous ADRs and provide an approach to minimize their occurrence.

Cutaneous ADRs in South Asia

During our literate review we could locate five studies from South Asia related to cutaneous ADRs. Mahboob and Haroon[7] evaluated 450 fixed drug eruption (FDE) patients to determine the causative drugs and found the ratio of men to women as 1:1.1. The main presentation of FDE was circular hyperpigmented lesions. Cotrimoxazole was the most common cause of FDE. Other drugs incriminated included tetracycline, metamizole, phenylbutazone, paracetamol, acetylsalicylic acid, mefenamic acid, metronidazole, tinidazole, chlormezanone, amoxycillin, ampicillin, erythromycin. FDE with diclofenac sodium, pyrantel pamoate, clindamycin, and albendazole was reported for the first time. FDE may have multiform presentations.[7]

A prospective study from Thailand[8] evaluated the types of drug eruption and the causative agents in a hospital-based population for a period of 1 year (from June, 1995 to May, 1996). One hundred and thirty-two patients were enrolled. The most common types of drug eruption were maculopapular eruption, fixed drug eruption, and urticaria. Antimicrobial agents were found to be the most common causative drugs, followed by antipyretic/anti-inflammatory agents and drugs acting on the central nervous system. The study identified that the new generation of antibiotics and antifungal agents were found to be a frequent cause of drug eruptions. New types of drug eruption, such as generalized exanthematous pustulosis and acral erythema, were also observed by the authors.[8]

A group of researchers from North India[9] carried out a prospective, hospital based study over a period of 6 years recording various cutaneous ADRs. A total of 500 patients with cutaneous ADRs were enrolled in the study. The most common types of cutaneous ADR patterns were maculopapular rash (34.6%), FDE (30%) and urticaria (14%). The drugs most often incriminated were antimicrobials (42.6%), anticonvulsants (22.2%) and NSAIDs (18%). Anticonvulsants were implicated in 41.6% of maculopapular rashes. Sulfonamides accounted for 43.3% and NSAIDs for 30.7% of FDE. Urticaria was caused mainly by NSAIDs (24.3%) and penicillins (20%). Anticonvulsants were responsible for 43.8% of life-threatening toxic epidermal necrolysis and Stevens Johnson syndrome.[9]

A group of investigators from South India[10] studied 113 patients with FDE. The causative drugs were identified and confirmed by provocation tests. A trimethoprim-sulfamethoxazole combination caused maximum incidence (36.3%), followed by tetracycline (15.9%), pyrazolones (14.2%), sulfadiazine (12.4%), dipyrine (9.3%), acetaminophen (7.9%), aspirin (1.7%), thiacetazone (0.88%), and levamizole (0.88%). The study indicated that the clinical pattern and distribution of lesions in FDE were

influenced by the drug in question, and the study of the pattern may provide useful information in identifying the most likely causative drug, especially when the details of the drugs are unknown.[10]

A prospective hospital-based study from South India[11] conducted between October 1, 2002 to September 30, 2003 evaluated the clinical spectrum of cutaneous ADRs in hospitalized patients and established a causal link between the drug and the reaction by using WHO causality definitions. A total of 56 patients were included in the study. Only drugs having certain and probable causal association with the reaction were considered for analysis. One reaction had certain causal association while 45 patients fell into the category of probable association. The most common types of ADRs were maculopapular rash (35%), followed by toxic epidermal necrolysis (TEN) (20%) and Stevens-Johnson syndrome (SJS) (15%). The drugs implicated were antiepileptics (44%), chemotherapeutic agents (32%) and NSAIDs (11%). Antiepileptics were responsible for causing the maximum number of maculopapular rash (56%), TEN (55%) and SJS (43%). The study concluded that the incidence of life-threatening cutaneous ADRs like SJS and TEN was higher compared to studies published abroad. Infrequently reported adverse reactions for newer drugs like leflunomide, cefotaxime and azithromycin were also detected in the study.[11]

Another study from South India[12] recruited ninety patients with cutaneous ADRs during the period 2001-2003. Hematological, biochemical and microbiological investigations were done in all of them. VDRL and HIV (ELISA) tests were performed where the underlying risk factors were present. Patch testing, intradermal testing and oral provocation tests were done wherever feasible. The mean age of the patients with cutaneous drug eruptions was 37.06 years. Most of them (52.2%) were in the age group of 20-39 years. The male to female ratio was 0.87: 1. The most common eruptions observed were fixed drug eruption (31.1%) and maculopapular rash (12.2%), and the most common causes were co-trimoxazole (22.2%) and dapsone (17.7%). The study concluded that the pattern of cutaneous ADRs and the drugs causing them is remarkably different in our population.[12]

A retrospective study[13] evaluated the clinical spectrum of cutaneous ADRs in hospitalized patients for 9 years (January, 1994 to December, 2002) and tried to establish a causal link between the drug and the reaction by using WHO causality definitions. Of the total 3541 patients, 404 (11.4%) were diagnosed as cutaneous ADRs, of which 52% were males and 48% females. A majority of the patients were in the age group of 21-40 years. Only drugs having certain and probable causal association to the reaction were considered for analysis (384). The most common type of ADR was maculopapular rash (42.7%), followed by SJS (19.5%) and fixed drug eruption (11.4%). The drug class implicated was antibiotics (45%), followed by antiepileptics (19%) and NSAIDs (19%). The study concluded that the incidence of life threatening cutaneous ADRs like SJS and TEN were found to be higher compared to studies published abroad. Antibiotics were the most commonly implicated drugs. A higher number of cutaneous ADRs were found to newer drugs like cephalosporins and fluroquinolones compared to previous studies.[13]

A study from a tertiary care teaching hospital in the Western part of Nepal[14] analyzed the cutaneous ADRs reported to the

Pharmacovigilance cell during a period of seven months (September, 2004 to March, 2005). A total of 45 cutaneous ADRs were reported among which maculopapular rash (15 reports) was the most common, followed by contact dermatitis (7 reports), fixed drug eruptions (6 reports) and erythema (4 reports). The study concluded that the pharmacovigilance program in the hospital should be strengthened and transformed to a full-fledged active reporting program.[14] A preliminary evaluation of the cutaneous ADRs reporting to the center revealed that the mean ± SD cost incurred by a patient in buying the medication for managing the cutaneous ADRs to be US$ 1.58 ±1.41.[15] This however, did not include the cost of hospitalization or other costs such as the consultation cost, indirect medical cost etc. incurred in the course of management of the ADRs.

A study from Nepal[16] reviewed the hospital admission records of patients admitted under various specialties of a teaching hospital for a period of four years. A total of 33 patients (male 11, female 22) with varying severity of cutaneous ADRs were admitted to the Departments of Medicine, Dermatology and Ophthalmology. These patients were in the age group 4-65 years (mean 34.5 years). Among them 6 had EM, 25 had SJS and 2 had TEN. The duration of their hospital stay varied from 4-19 days (mean 11.5 days). Reactions in 15 patients appeared to be due to antibiotics (sulfonamides, penicillins, quinolones), in 10 patients due to anticonvulsants (carbamazepine, 5; phenytoin, 4; phenobarbitone, 1), in 4 patients due to NSAIDs and in 4 cases the causes were unidentified. The study concluded that the patients with severe cutaneous ADRs have multisystem involvement and a multidisciplinary approach is necessary for their management. The authors concluded that it is essential to develop protocol/guidelines for the management of severe cutaneous ADRs in their setup.[16]

Pathogenesis of cutaneous ADRs

Untoward cutaneous response to drugs can arise as a result of non-immunologic or immunologic mechanisms. Immunologic reactions require activation of host immunologic pathways and are designated as drug allergy. Drug reactions occurring through nonimmunologic mechanisms may be due to activation of effector pathways, over dosage, cumulative toxicity, side effects and interaction between drugs or metabolic alterations. Exacerbation of preexisting dermatologic conditions or inherited protein or enzyme deficiencies may also be responsible. It is often not possible to specify the responsible drug or pathogenic mechanism because the skin responds to a variety of stimuli through a limited number of reaction patterns. The mechanism of many drug reactions is unknown.[17]

Risk factors for ADRs

The various risk factors for ADRs are listed below.

1. Age Although relatively few data are available, adverse events are more frequently encountered at the extremes of age. In the neonate, the liver and kidney enzymes necessary for drug metabolism and elimination are not optimally functional and clearance of many drugs is less than in adults. In the elderly, changes in liver and kidney function may decrease drug elimination.[18]

2. Sex Women are reported to have a 50 percent higher rate of adverse effects than men.[19] This is explained by the fact that there are frequent periods in a woman's life (menarche, pregnancy, lactation and menopause) when there is alteration of pharmacokinetics of drugs.[20] Also women may more frequently seek medical attention than men.

3. Past history of reactions Reports suggest that patients with past history of ADRs are more likely to experience further ADRs. In one study 28 percent of patients who developed ADRs had a previous history of adverse drug reaction.[21]

4. Genetic factors Genetic factors may be important. This may include polymorphism in drug metabolism and other genetic variations. The association of Stevens-Johnson syndrome-toxic epidermal necrolysis (SJS-TEN) and drug hypersensitive syndrome to specific human leukocyte antigen (HLA) subtypes has been reported.[21]

5. Environmental factors Infectious agents, sun exposure etc. may precipitate severe cutaneous drug reactions.[22]

Recognizing adverse drug reactions

For estimating the probability that a specific drug is responsible for an ADR, several scales have been developed.[23-25] The most widely used is the Naranjo algorithm.[25] It has good internal reliability and assessment can be carried out quickly; it consists of ten questions about the probability that the reported ADR is due to a particular drug. A score of 1 to 4 points indicates that an ADR is considered possible, 5 to 8 probable, and 9 or more definite. The criteria to be considered in diagnosing severe

cutaneous adverse reactions and their causes are as follows.[2]

1. Alternative causes should be excluded, especially infections, since many infectious illness are difficult to distinguish clinically from the adverse effects of drugs.

2. The interval between the introduction of a drug and the onset of a reaction should be examined.

3. Any improvement after drug withdrawal should be noted.

4. The physician should determine whether similar reactions have been reported with the same compounds.

5. Any reactions on re-administration of the drug should be noted.

Types of ADRs

ADRs may be due to immunological or non-immunological mechanisms, the latter being more common. ADRs may be predictable (type A) or unpredictable (type B).[26-29]

Type-A (Predictable reactions) These are due to known pharmacological actions of the drugs, are usually dose related and occur in otherwise normal individuals. Predictable reactions include toxicity or overdose, side effects, drug interactions and secondary effects.

Type-B (Unpredictable reactions) These are dose independent, not related to pharmacological actions of the drug and may have a genetic basis. These reactions are divided into three categories: intolerance,

idiosyncratic reaction and hypersensitivity reaction.

Type C reactions include those associated with chronic therapy.

Type D reactions consist of delayed reactions e.g. carcinogenesis and teratogenesis.

Clinical manifestations of cutaneous ADRs

Cutaneous ADR can present in one of the following forms.

Urticarial reactions

Urticaria, sometimes accompanied by angioedema, probably is one of the most common cutaneous manifestations of allergic drug reactions. Urticaria or angioedema occurring within minutes of drug ingestion is termed as immediate reaction. Chronic urticaria is used to describe urticaria that lasts for more than six weeks.[30] Urticaria can represent an IgE mediated hypersensitivity reaction leading to release of mediators like histamine, platelet activating factor (PAF) and leukotriene C_4 which are pathophysiologic markers of urticaria. Penicillin is the most common drug but other antibiotics like sulphonamides, cephalosporins and tetracyclines, as well as diuretics, analgesics and antihypertensives may be responsible. Urticaria can also be IgE independent complement mediated reaction, or due to direct degranulation of mast cells by drugs like aspirin, radio contrast media, d-tubocurarine etc.

Urticarial rashes manifest as severely pruritic, circumscribed, raised, edematous and erythematous wheals widely scattered on the body. It may accompany systemic anaphylaxis or serum sickness. Urticarial lesions rarely persist for more than 24 hours.[31-33] Angioedema involving edema of the deep dermis or subcutaneous and submucosal areas is less commonly seen than urticaria as an adverse drug reaction; the exception being ACE inhibitors in which angiodema is more frequent during initial weeks of therapy.[34]

Exanthematous (maculopapular) rash

This is probably the most frequent type of skin reaction to systemically administered drugs and presents as a generalized fine maculopapular eruption resembling measles. The distribution is generally bilaterally symmetrical involving the trunk and extremities. Maculopapular eruptions usually fade with desquamation, sometimes with post inflammatory hyperpigmentation.[35]

Erythema multiforme

The skin eruption of erythema multiforme (EM) is characterized by the acute appearance of annular erythematous lesions, most having a central erythematous papule or bulla that gives the appearance of a marksman's target to the lesions. The so called "target lesion" or "iris lesion" are often generalized and can involve the palms and soles. EM minor is the term used for eruptions that involve the skin and/or one mucosal surface without systemic symptoms. Approximately 90% of these cases are associated with herpes simplex eruptions, and herpes simplex DNA has been identified in the EM lesions of 75% of patients sampled in one study.[36] There are, however, reports of EM in response to drugs, with long-acting sulfonamides being most frequently implicated.[37] Barbiturates, sulindac, and fenoprofen are also frequent suspects.[38] Whereas the pathogenesis of EM is not firmly established, an immune complex-mediated vasculitis may be implicated, based on studies

on herpes simplex-associated and mycoplasma pneumonia-associated EM.[39]

The other type, EM major (Stevens-Johnson syndrome) is regarded by some as a more severe form of EM characterized by erosive mucous membrane lesions as well as systemic symptoms of fever and malaise. However, the recent evidence linking most cases of EM with herpes simplex adds increasing support to regarding erythema multiforme as a separate entity from Stevens-Johnson syndrome.[40] The incidence of Stevens-Johnson syndrome ranges from 1.2 to 6 per million per year and carries around 5% mortality.[41] Sulfonamides, anticonvulsants, allopurinol, pyrazolone derivatives, oxicams, and chlormezanone are the drugs most frequently associated with Stevens-Johnson syndrome.

Toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN) is a severe cutaneous reaction clinically separate from Stevens-Johnson syndrome and is characterized by diffuse erythema with tenderness, fever, and malaise followed by widespread sloughing of the epidermis resembling a scald injury. Mucous membranes show erythema, erosions and bullae. The incidence of TEN ranges from 0.4 to 1.2 per million per year, but the disorder is fatal in about 30% of cases.[41] Although TEN is associated with a variety of etiologic factors,[42] drugs that are definitely implicated include sulfonamides, butazones, hydantoins, barbiturates and penicillin.[38]

Contact dermatitis

It is an acute or chronic inflammation, often asymmetric or oddly shaped, produced by substances coming in contact with the skin or extravasated into the skin and causing toxic (irritant) or allergic reactions. Contact dermatitis ranging from transient redness to severe swelling with bullae, pruritus and vesiculation are common. Any skin surface exposed to an irritant or sensitizing substance (including airborne ones) may be involved. Typically, the dermatitis is limited to the site of contact but may later spread. Contact dermatitis is known to occur with topical antibiotics like penicillin, sulfonamides, neomycin, antihistamines (diphenhydramine, promethazine), anesthetics (benzocaine), antiseptics (thiomersal, hexachlorophene) etc.[43]

Exfoliative dermatitis

In this condition erythema and scaling occurs involving more than 90% of the body surface. It is an end stage reaction pattern to various stimuli including diseases, malignancies and drugs. The drugs commonly implicated include antiepileptics, antibiotics, heavy metals, sulfa drugs, salicylates etc. Debility and death may occur due to loss of skin function and alteration of internal metabolism.[17]

Fixed drug eruption

FDEs are characterized by the fact that they tend to occur at the same site in a particular patient each time the drug is administered. FDEs are seen with drugs like barbiturates, chlordiazepoxide, dapsone, griseofulvin, indomethacin, phenopthalein, phenytoin, quinine, salicylates, sulfonamides, tetracyclines, etc. Once the drug has been stopped, the lesions heal with pigmentation, which may be the only physical sign at the time of presentation.[44]

Miscellaneous cutaneous ADRs

Other forms of cutaneous ADRs include lichenoid eruptions, photosensitivity, vasculitis, skin necrosis, psoriasiform eruptions, pityriasiform eruptions, acneiform

eruptions, erythema nodosum, bullous eruptions, peripheral cyanosis, gangrene etc.

Diagnosis of cutaneous ADRs

A diagnosis can often be made from the history and physical examination. Clinical criteria that may be helpful in defining a cutaneous ADR include: 1) other causes for the eruption, such as viral exanthema, should be excluded; 2) a temporal relationship between drug use and onset of the reaction should exist; 3) improvement should be noted following drug cessation; 4) reactivation upon re-challenge of the drug should be noted; and 5) the cutaneous reaction is known to be associated with the drug in question. Skin biopsy, and estimation of drug levels in blood, especially in cases associated with over dosage or non-allergic type of reaction also may be done. In selected cases, oral re-exposure, or prick or scratch tests with the offending drug may be carried out, after hospitalization.[45]

Differential diagnosis of cutaneous ADRs

The differential diagnosis of cutaneous drug reactions depends upon its morphological presentation. The differential diagnoses of commonly seen cutaneous ADRs are discussed below.

1. Urticaria and angioedema
This reaction pattern can occur due to many other conditions like insect bite, bee or wasp sting, exposure to pollen, paint, fumes, etc. A proper history may be able to pinpoint the precipitating factor

2. Acneiform drug eruptions
This may be confused with acne vulgaris. Coal tar, occupational friction etc. can also cause acneiform eruptions.

3. Erythema multiforme and SJS
Other than drugs, viruses like herpes simplex are well known to cause target lesions and maculopapular rashes resembling drug-induced erythema multiforme. Sometimes, staphylococcal scalded skin syndrome (SSSS) may be mistaken for SJS.

4. Erythema nodosum
Tuberculosis, streptococcal throat infections, sarcoidosis and other infections are very common causes of erythema nodosum.

5. Toxic epidermal necrolysis
Sometimes, SSSS may be confused with TEN. In SSSS, oral mucosal lesions are not seen and it usually has a cephalocaudal progression. SSSS is normally seen in children, whereas TEN is more common in adults. In cases of doubt, skin biopsy confirms the diagnosis. The cleavage plane of SSSS is intraepidermal, whereas there is dermo-epidermal separation in TEN.

6. Maculopapular drug rash
A very common differential diagnosis is viral exanthem. As NSAIDs, anticold remedies, antibiotics are given for viral fever and common cold, sometimes it is difficult to attribute the cause for a maculopapular rash, as viral exanthemas and maculopapular rash look similar. But viral exanthem is usually accompanied by fever, oral enanthem, cephalocaudal progression and palmoplantar erythema. Drug rash, on the other hand is more pruritic, and has no cephalocaudal progression or associated enanthem.

7. Fixed drug eruption
In its acute stage with bullae and edema, FDE may be mistaken for a bullous skin disease like bullous impetigo, bullous insect bite reaction, traumatic bullae and bullous pemphigoid. FDE

normally heals by residual post inflammatory pigmentation and this can be mistaken for other pigmentary disorders of the skin like post inflammatory pigmentation following burns, insect bite, healed eczema etc.

8. Lichenoid drug eruption

This can be mistaken for lichen planus, a papulosquamous skin disorder. A thorough drug history and skin biopsy is helpful in differentiating lichenoid eruption from lichen planus.

9. Exfoliative dermatitis

This condition is usually secondary to other skin disorders like psoriasis and contact dermatitis, internal disease like malignancies or due to drugs. Drug induced exfoliative dermatitis is acute in onset and responds well to systemic steroids whereas disease induced exfoliative dermatitis is more chronic and there is a slower response to therapy. Skin biopsy may reveal underlying skin disease or malignancy.

Management of cutaneous ADRs

Mild cases are managed by immediate cessation of the offending agent combined with use of topical corticosteroids, antipruritic agents and oral antihistamines. For moderate to severe cases, systemic steroids and special treatment like management in a burns unit, taking care of strict asepsis, debridement of necrotic tissue etc., may be necessary. If a severe reaction is suspected, immediate withdrawal of all potential offending agents is the most effective mode of therapy. Patients with extensive involvement should be cared for as a 'burn patient' with fluid resuscitation, infection control measures, and nutritional support in a hospital burn-unit setting.[40]

Strategies to prevent cutaneous ADRs

An effective strategy to prevent the occurrence of ADRs is always preferred. Some of the measures that may reduce the occurrence of cutaneous ADRs are listed below.

1. Avoid polypharmacy.

2. Prescribe drugs, which have been known to cause cutaneous ADRs, only if extremely necessary.

3. Obtain history of skin reactions in the past.

4. Educate the patients regarding common early symptoms of drug reactions (e.g. erythematous rash, edema, urticaria, mucosal erosions, itching, burning of skin etc.) especially during start of a therapy.

5. A patient with cutaneous ADRs should be provided with a card/bracelet inscribed with the name (s) of offending agents.

Conclusion

Cutaneous ADRs vary in their appearance, rapidity of onset, severity, potential sequelae, and underlying immunopathologic mechanisms. Certain classes of drugs such as antibiotics and anticonvulsants are most often implicated. However, any drug can cause a reaction. When a cutaneous ADR is suspected, the causative drug must be identified and withdrawn. Depending on the nature of the drug eruption, symptomatic treatment may be accompanied by local skin care and, if indicated, immunomodulating therapy with corticosteroids to reduce the severity of the skin reaction. In rare instances in which therapy with the offending drug is deemed essential and no alternative therapeutic agent is

available, an offending drug may be continued or reintroduced using previously published protocols.

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