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內文：

### Abstract

**Aim:** The aim of this comprehensive review is to present an update to our previous review about drug-induced oral reactions. All drugs that may cause adverse effects in the mouth and related structures are reviewed.

**Background:** The mouth and associated structures can be affected by many drugs or chemicals. Drug reactions can be categorized as to the parts of the oral complex such as the oral mucosa and tongue, periodontal tissues, dental structures, salivary glands, cleft lip and palate, muscles, and nerves.

**Review Results:** This review suggests the number of drugs and chemicals that can produce adverse or toxic reactions in the oral cavity are on the rise. An updated listing of offending drugs is provided along with current strategies for dealing with adverse reactions.

**Conclusion:** Clinicians must constantly update their knowledge of drugs used by their patients. Attention must be paid to their toxic and unwanted effects that in many cases may be similar to characteristics of common diseases.

**Clinical Significance:** Dentists and specialists of oral diseases should be aware of adverse drug oral reactions for better diagnosis of oral diseases, administration of drugs, and patient compliance during drug therapy

### Introduction

In theory, all drugs are capable of inducing adverse side effects, the three most frequent oral side-effects encountered were xerostomia, dysgeusia, and stomatitis with prevalence rates of 80.5%, 47.5%, and 33.9%. The 2003 review of drug-induced oral reactions published by Abdollahi and Radfar included the subjects:

<ul style="list-style-type: none"> <li>• Alveolar osteitis</li> <li>• Angioedema</li> <li>• Aphthous stomatitis</li> <li>• Black hairy tongue</li> <li>• Burning mouth syndrome</li> <li>• Changes in dental structure</li> <li>• Cheilitis</li> <li>• Discoloration of oral mucosa and teeth</li> </ul>	<ul style="list-style-type: none"> <li>• Erythema multiforme</li> <li>• Gingival hyperplasia</li> <li>• Glossitis</li> <li>• Halitosis</li> <li>• Lichenoid eruptions</li> <li>• Muscular and neurological disorders</li> <li>• Oral allergic reactions</li> </ul>	<ul style="list-style-type: none"> <li>• Oral infections</li> <li>• Oral ulceration</li> <li>• Postmortem pink-red coloration</li> <li>• Side effects in salivary glands</li> <li>• Stomatodynia</li> <li>• Taste disturbance</li> <li>• Vesiculo-bullous lesions</li> </ul>
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## Oral Allergic Reactions

Systemic medications can cause allergic reactions in the mouth as a fixed drug eruption called **stomatitis medicamentosa**. Oral lesions can also be erosive and ulcerated. They may occur on the **gingiva** and **palate**, although the **buccal mucosa**, **lips**, and **tongue** are more frequently involved. Drugs with potential to cause fixed drug eruptions are shown below.

<ul style="list-style-type: none"> <li>• Ampicillin</li> <li>• Barbiturates</li> <li>• Chlorhexidine</li> <li>• Dapsone</li> <li>• Gold</li> <li>• Ibuprofen</li> <li>• Indomethacin</li> </ul>	<ul style="list-style-type: none"> <li>• Lidocaine</li> <li>• NSAIDs</li> <li>• Penicillamine</li> <li>• Salicylates</li> <li>• Sulphonamides</li> <li>• Tetracyclines</li> </ul>
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Oral contact allergic reactions or stomatitis venenata has increased in recent years because of the increased **use of oral hygiene products, esthetics related products, dental restorative materials**, and the establishment of infection control procedures that mandate **the wearing of latex gloves** for dental treatment procedures. The **gingiva** is often the only site of reaction or the most severely involved, perhaps because the antigen is in intimate contact with the gingiva during toothbrushing. In most instances the reactions appear to be induced by the flavoring agents in the dentifrices, often **cinnamic aldehyde**. Compounds with potential to cause oral contact allergic reactions are shown below.

<ul style="list-style-type: none"> <li>• Alendronate</li> <li>• Antibiotics</li> <li>• Antiseptic lozenges</li> <li>• Chewing gum</li> <li>• Cosmetics</li> <li>• Dental materials (amalgam, steel wires, beryllium, palladium, platinum, acrylic components)</li> </ul>	<ul style="list-style-type: none"> <li>• Food additives</li> <li>• Iodine</li> <li>• Mouthwashes</li> <li>• Toothpastes (especially those containing cinnamaldehyde, formalin and herbal components)</li> <li>• Topical anesthetics</li> <li>• Topical steroids</li> </ul>
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## Aphthous-Like Ulcers

Ulcers resembling recurrent aphthous stomatitis but have systemic causes are often termed aphthous-like ulcers. Recurrent aphthous stomatitis (also referred to as aphthae or canker sores) is one of the **most common oral ailments**. The term “recurrent aphthous stomatitis” should be reserved for recurrent ulcers **confined to the mouth and seen in the absence of any systemic cause**. Drugs with potential to cause aphthous-like ulcers are shown below.

<ul style="list-style-type: none"> <li>• Alendronate</li> <li>• Azathiopurine</li> <li>• <b>Beta-blockers</b></li> <li>• Captopril</li> <li>• Cyclosporine</li> <li>• Docetaxel</li> <li>• Fluoxetine</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Gold compounds</b></li> <li>• Imiquimod</li> <li>• Indinavir</li> <li>• Interferons</li> <li>• Losartan</li> <li>• Nicorandil</li> </ul>	<ul style="list-style-type: none"> <li>• <b>NSAIDs</b></li> <li>• Olanzapine</li> <li>• Penicillamine</li> <li>• Sertraline</li> <li>• Sulfonamides</li> <li>• Tiotropium bromide</li> </ul>
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### Burning Mouth Syndrome

Burning mouth syndrome (BMS) is synonymous with stomatodynia, oral dysaesthesia, glossodynia, glossopyrosis, and stomatopyrosis characterized by oral mucosa pain, with or without inflammatory signs, and without a specific lesion. The pain feels like a moderate to severe burning sensation occurring more frequently on the tongue but can also occur on the gingiva, lips, and jugal (malar) mucosa. It can worsen during the day as a result of stress and fatigue, excessive speaking, or by ingesting spicy/hot foods. The burning can be diminished with cold food and leisure. This syndrome may occur due to **xerostomia** or **radiotherapy**; **endocrine disease** such as diabetes mellitus, hypothyroidism, and menopause; **medication**; **nutritional deficiencies** including iron, vitamin B complex, folic acid and zinc; neuralgia; **dental prostheses**; **allergy**; **infection**; and **psychiatric disorders** such as depression and anxiety. **Angiotensin converting enzyme inhibitors (ACEIs)** are a class of medications that can cause BMS. A list of drugs that can induce BMS is shown below.

<ul style="list-style-type: none"> <li>• ACEIs</li> <li>• Antiretroviral drugs</li> <li>• Cephalosporines</li> <li>• Chloramphenicol</li> </ul>	<ul style="list-style-type: none"> <li>• Clonazepam Gabapentin</li> <li>• Hormone replacement therapy (estradiol, didrogestrone)</li> <li>• Penicillin</li> <li>• <b>Tricyclic antidepressants</b></li> </ul>
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### Glossitis

Glossitis is inflammation of the tongue characterized by swelling and intense pain that **may be referred to the ears**. Drugs having the potential to cause glossitis are shown below.

<ul style="list-style-type: none"> <li>• Alkylating agents</li> <li>• Atrovastatin</li> <li>• Benzodiazepines</li> <li>• Bleomycin</li> <li>• Captopril</li> <li>• Carbamazepine</li> <li>• Cephalosporines</li> <li>• Chloramphenicol</li> <li>• Chlorhexidine</li> <li>• Clarithromycin</li> <li>• Clomipramine</li> <li>• Corticosteroids</li> <li>• Cyclosporine</li> <li>• Doxepin</li> </ul>	<ul style="list-style-type: none"> <li>• Enalapril</li> <li>• Etidronate</li> <li>• Fluoxetine</li> <li>• Fluvoxamine</li> <li>• Gabapentin</li> <li>• Gold compounds</li> <li>• Imipenem/cilastatin</li> <li>• Lansoprazole</li> <li>• Mefenamic acid</li> <li>• Mercaptopurine</li> <li>• Methotrexate</li> <li>• Metronidazole</li> <li>• Mianserin</li> <li>• NSAIDs</li> </ul>	<ul style="list-style-type: none"> <li>• Olanzapine</li> <li>• Penicillamine</li> <li>• Penicillins</li> <li>• Rivastigmine</li> <li>• Serteraline</li> <li>• Sildenafil</li> <li>• Sulfonamides</li> <li>• Tacrine</li> <li>• Tetracyclines</li> <li>• Triamterene</li> <li>• Tricyclic antidepressants</li> <li>• Trihexyphenidyl</li> <li>• Venlafaxine</li> <li>• Xerostomizing medications (table 13)</li> </ul>
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### Erythema Multiforme

Erythema multiforme (EM) is an acute reactive mucocutaneous inflammatory and hypersensitivity reaction characterized by a skin eruption, with symmetrical erythematous edematous or bullous lesions of the skin or mucous membranes. More than half the cases have no known cause, while half are caused by medications, infections, immunotherapy, or illnesses. Only **4% of EM reactions are caused by drugs**. Drugs with potential to cause EM are shown below.

<ul style="list-style-type: none"> <li>• Acarbose</li> <li>• Albendazole</li> <li>• Allopurinol</li> <li>• Antimalarials</li> <li>• Aspirin</li> <li>• Astemizole</li> <li>• Atovaquone</li> <li>• Barbiturates</li> <li>• Bupropion</li> <li>• Busulphan</li> <li>• Captopril</li> <li>• Carbamazepine</li> <li>• Carvedilol</li> <li>• Celecoxib</li> <li>• Cephalosporins</li> <li>• Chlorpropamide</li> <li>• Ciprofloxacin</li> <li>• Clindamycin</li> <li>• Clofibrate</li> <li>• Cocaine</li> <li>• Codein</li> <li>• Corticotropin</li> </ul>	<ul style="list-style-type: none"> <li>• Famciclovir</li> <li>• Furazolidone</li> <li>• Furosemide</li> <li>• Gabapentin</li> <li>• Ginseng</li> <li>• Glipizide</li> <li>• Glucagon</li> <li>• Gold compounds</li> <li>• Griseofulvin</li> <li>• Hetastarch</li> <li>• Immune globulin</li> <li>• Indapamide</li> <li>• Iodine-containing mouth washes</li> <li>• Itraconazole</li> <li>• Ketoconazole</li> <li>• Ketorolac</li> <li>• Lamotrigine Lenograstim</li> <li>• Loperamide</li> <li>• Methazolamide</li> <li>• Mianserin</li> <li>• Micafungin</li> <li>• Minoxidil</li> </ul>	<ul style="list-style-type: none"> <li>• Prednisolone</li> <li>• Propranolol</li> <li>• Propylthiouracil</li> <li>• Protease inhibitors</li> <li>• Proton pump inhibitors</li> <li>• Pyrazinamide</li> <li>• Pyrimethamine</li> <li>• Rifampin</li> <li>• Rifampicin</li> <li>• Rivastigmine</li> <li>• Rofecoxib</li> <li>• Roxatidine</li> <li>• Sertraline</li> <li>• Sulindac</li> <li>• Sulphonamides</li> <li>• Suramin</li> <li>• Tacrolimus</li> <li>• Tadalafil</li> <li>• Terbinafine</li> <li>• Tetracyclines</li> <li>• Thalidomide</li> <li>• Theophylline</li> <li>• Thiabendazole</li> </ul>
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<ul style="list-style-type: none"> <li>• Cosyntropin</li> <li>• Cotrimoxazole</li> <li>• Cycloserine</li> <li>• Diclofenac</li> <li>• Diflunisal</li> <li>• Diltiazem</li> <li>• Dolcetaxel</li> <li>• Doxycycline</li> <li>• Erythromycin</li> <li>• Estrogens/Progestins</li> <li>• Etodolac</li> <li>• Etoposide</li> <li>• Ethambutol</li> </ul>	<ul style="list-style-type: none"> <li>• Nabumetone</li> <li>• Nefazodone</li> <li>• NSAIDs</li> <li>• Nystatin</li> <li>• Ofloxacin</li> <li>• Oxaprozin</li> <li>• Oxcarbazepine</li> <li>• Penicillamine</li> <li>• Penicillins</li> <li>• Pentamidine</li> <li>• Phenothiazines</li> <li>• Phenylbutazone</li> <li>• Phenytoin</li> </ul>	<ul style="list-style-type: none"> <li>• Thioridazine</li> <li>• Tiagabine</li> <li>• Tiapride</li> <li>• Tolbutamide</li> <li>• Tolmetin</li> <li>• Trazodone</li> <li>• Tropicamide</li> <li>• Valproic acid</li> <li>• Vancomycin</li> <li>• Varicella virus vaccine</li> <li>• Verapamil</li> <li>• Zonisamide</li> </ul>
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### Oral Ulceration

Ulceration is a breach in the oral epithelium, which typically **exposes nerve endings** in the underlying lamina propria, resulting in **pain or soreness**, especially when eating spicy foods or citrus fruits. Ulcers and erosions can also be a final common manifestation of a spectrum of conditions. These conditions include the following:

- Epithelial damage resulting from trauma
- An immunological attack as in lichen planus
- Pemphigoid or pemphigus
- Damage due to an immune defect as in HIV disease and leukemia
- Infections such as herpes viruses
- Tuberculosis and syphilis
- Cancer
- Nutritional defects such as vitamin deficiencies
- Some gastrointestinal diseases
- Medications

Drugs and chemicals that may cause local irritation and ulceration of the mouth include those listed in the following table.

<ul style="list-style-type: none"> <li>• Anticancer drugs</li> <li>• Aspirin</li> <li>• Cocaine</li> <li>• Ergotamine Tartrate</li> <li>• Hydrogen peroxide</li> </ul>	<ul style="list-style-type: none"> <li>• Isoproterenol</li> <li>• Lithium</li> <li>• NSAIDs</li> <li>• Pancreatin</li> <li>• Paraquat</li> </ul>	<ul style="list-style-type: none"> <li>• Potassium chloride</li> <li>• Selegiline</li> <li>• Tetracyclines</li> <li>• Toothache solutions (menthol, phenol, clove oil, camphor and chloroform)</li> </ul>	
<ul style="list-style-type: none"> <li>• Anti HIV drugs</li> <li>• Antineoplastics</li> <li>• Alendronate</li> <li>• Allopurinol</li> <li>• Alprazolam</li> <li>• Aspirin</li> <li>• Atrovastatin</li> </ul>	<ul style="list-style-type: none"> <li>• Clonazepam</li> <li>• Codeine</li> <li>• Cyclosporine</li> <li>• Disopyramide</li> <li>• Enalapril</li> <li>• Erythromycin</li> <li>• Fluconazole</li> </ul>	<ul style="list-style-type: none"> <li>• ibuprofen</li> <li>• Imatinib</li> <li>• Imipramine</li> <li>• Indomethacin</li> <li>• Lamotrigine</li> <li>• Levamisole</li> <li>• Lithium</li> </ul>	<ul style="list-style-type: none"> <li>• Penicillamine</li> <li>• Penicillins</li> <li>• Phenytoin</li> <li>• Proguanil</li> <li>• Promethazine</li> <li>• Propranolol</li> <li>• Propylthiouracil</li> </ul>

<ul style="list-style-type: none"> <li>• Azathiopurine</li> <li>• Barbiturates</li> <li>• Captopril</li> <li>• Chlorambucil</li> <li>• Chloramphenicol</li> <li>• Chloroquine</li> <li>• Chlorpromazine</li> <li>• Clofibrate</li> </ul>	<ul style="list-style-type: none"> <li>• Fluoxetine</li> <li>• Ganciclovir</li> <li>• Gefitinib</li> <li>• Gentian violet</li> <li>• Gold compounds</li> <li>• Hydralazine</li> <li>• Hydroxyurea</li> </ul>	<ul style="list-style-type: none"> <li>• Mesalamine</li> <li>• Methimazole</li> <li>• Methotrexate</li> <li>• Metronidazole</li> <li>• Mitomycin</li> <li>• Naproxen</li> <li>• Olanzapine</li> </ul>	<ul style="list-style-type: none"> <li>• Quinidine</li> <li>• Streptomycin</li> <li>• Sulfonamides</li> <li>• Terbutaline</li> <li>• Tetracycline</li> <li>• Venlafaxine</li> <li>• Warfarin</li> </ul>
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### Vesiculo–Bullous Lesions

The exact mechanism of this tissue reaction is unclear, but it appears to be the consequence of a direct irritant. Patients using **steroid inhalers** for more than five years are more prone to the development of oral blistering. This type of reaction has also been reported for **naproxen** and **penicillamine**.

### Oral Lichenoid Reactions

Lichen planus is a **chronic systemic disease** of established immune-mediated pathogenesis. It commonly involves the mucosa of the oral cavity but can involve other sites, such as the skin, vulvar and vaginal mucosa, the glans penis, the scalp, and the nails. Unlike true oral lichen planus, drug-induced oral lichenoid eruptions **disappear after drug withdrawal**. Such drugs are listed in the following table.

<ul style="list-style-type: none"> <li>• Allopurinol</li> <li>• Amiphenazole</li> <li>• Angiotensin-converting enzyme inhibitors</li> <li>• Antibiotics</li> <li>• Antiretrovirals</li> <li>• Arsenical Compounds</li> <li>• β-blockers</li> <li>• Bismuth</li> <li>• Chloroquine</li> <li>• Chlorpropamide</li> </ul>	<ul style="list-style-type: none"> <li>• Furosemide</li> <li>• Gold compounds</li> <li>• Hydroxychloroquine</li> <li>• Lithium Carbonate</li> <li>• Mepacrine</li> <li>• Mercury (Amalgam)</li> <li>• Methyldopa</li> <li>• NSAIDs</li> <li>• Palladium</li> <li>• Para-amino salicylic acid</li> <li>• Penicillamine</li> </ul>	<ul style="list-style-type: none"> <li>• Phenothiazines</li> <li>• Propranolol</li> <li>• Quinine</li> <li>• Quinidine</li> <li>• Streptomycin</li> <li>• Tetracyclines</li> <li>• Thalidomide</li> <li>• Thiazides</li> <li>• Tolbutamide</li> </ul>
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### Color Changes of the Oral Mucosa and Teeth

#### Mucosal Pigmentation

Extrinsic discoloration

- Use of tobacco or betel nut.
- Consumption of colored foods or beverages (such as liquorice, beet root, red wine, coffee, and tea).
- Use of drugs (such as chlorhexidine, iron salts, crack, cocaine, minocycline, bismuth subsalicylate, and lansoprazole).

Intrinsic mucosal hyperpigmentation

- Amalgam or other tattoo
- Nevus

- Melanotic macule
- Neoplasms (e.g., malignant melanoma or Kaposi's)
- Pigmentary incontinence
- Peutz-Jegher's syndrome
- Racial pigmentation
- Localized irritation such as the use of tobacco or betel nuts
- Drugs such as antimalarials and oral contraceptives
- Pregnancy
- Addison's disease

Drugs and chemicals with potential to cause oral pigmentation are listed below.

Drug/chemical	Color	Site
Amalgam	Gray	Gingiva
Amalgam	Brown (Tattoo)	Tongue
Aminopyrine	Brown	Tongue
Amodiaquine	Blue-gray/black	Palate
Arsenic	Brown	Tongue
Aspirin	White	-
Bismuth	Blue-gray/Blue-black/Brown	Gum lines/mucosa/tongue
Bromine	Brown	Tongue
Busulfan	Brown	Mucosa
Chlorhexidine	White/Brown	Tongue
Chloroquine	Blue-gray	Hard Palate, gingiva, lip
Coal	Metal dust dark	Mucosa
Copper salts	Blue-green	Gum lines
Cyclophosphamide		-
Doxorubicin	Dark/Brown	Mucosa/Tongue
Gold	Purple	Gingiva
Heroin inhalation	Dark macular patch	Tongue
Iron	Dark	-
Lansoprazole	Yellow	Tongue
Lead	Blue-gray/Blue	Gum Lines/Tongue
Manganese	Dark	-
Mepacrine	Yellow	Mucosa
Mercury	Blue-gray/Blue-black	Gum Line/Buccal
Methyldopa	Darkening	Tongue
Oral contraceptives	Dark	Mucosa

Drug/chemical	Color	Site
Quinacrine	Gray/Brown	Palate/Tongue
Quinidine	Blue-Black	Palate
Quinine	Brown	-
Silver Salts	Gray	Gingiva
Thallium	Blue-gray	Gum Lines
Tin	Dark	-
Tobacco	Hazy gray or Brown	-
Vanadium	Green	Tongue
Zidovudine	Dark	Soft Palate, Gingiva, Lips, Tongue

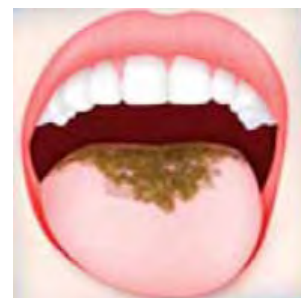
**Dental Discoloration**

Tetracycline can cause the most common distracting, generalized type of intrinsic discoloration. Drugs and chemicals with potential to cause tooth discoloration are listed in the following table.

Drugs/Chemical	Color
Betel leaves (areca)	Red to black
Cadmium	Yellow ring
Cayenne	Black
Chlorhexidine	Yellow-brown
Chlortetracycline	Gray-brown
Ciprofloxacin	Green
Co-amoxiclav	Yellow or gray brown
Copper salts	Green
Doxycyclin	Yellow
Essential oils	Yellow-brown
Fluoride	White-brown
Iron salts in liquid form	Black
Isoproterenol	Chalky white

**Black Hairy Tongue (Lingua villosa nigra)**

An elongation of the **filiform papillae** of the tongue forms hair-like overgrowth which becomes stained brown or black due to the proliferation of chromogenic microorganisms. Drugs and chemicals with potential to cause black tongue include those listed below.





<ul style="list-style-type: none"> <li>• Amitriptyline</li> <li>• Benzotropine</li> <li>• Cephalosporines</li> <li>• Chloramphenicol</li> <li>• Chlorophyll trouches</li> <li>• Clarithromycin</li> <li>• Clomipramine</li> <li>• Clonazepam</li> <li>• Corticosteroids</li> <li>• Desipramine</li> </ul>	<ul style="list-style-type: none"> <li>• Fluoxetine</li> <li>• Griseofulvin</li> <li>• Imipramine</li> <li>• Lansoprazole</li> <li>• Methyldopa</li> <li>• Maprotilline</li> <li>• Nortriptyline</li> <li>• Olanzapine</li> <li>• Penicillins</li> </ul>	<ul style="list-style-type: none"> <li>• Sodium perborate</li> <li>• Sodium peroxide</li> <li>• Streptomycin</li> <li>• Sulfonamides</li> <li>• Tobacco</li> <li>• Tetracyclines</li> <li>• Thiothixene</li> <li>• Tranylcypramine</li> <li>• Vegetable dyes</li> </ul>
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### Oral Mucositis

Oral mucositis is a common toxicity associated with both head and neck radiation and chemotherapy used for the treatment of cancer. The early clinical sign of chemotherapy-induced mucositis is erythema presenting, burning and intolerance of spicy foods at about four to five days following chemotherapy infusion. Seven to ten days after chemotherapy ulcers may develop with marked discomfort often requiring opioid intervention and, in many cases, causing patients to alter their diet. Chemotherapy-induced mucositis lasts approximately one week and generally heals spontaneously by 21 days after infusion. A healthy gingival status as well as good oral hygiene during chemotherapy is associated with a lower incidence and severity of mucositis.

<b>題號</b>	<b>題目</b>
<b>1</b>	Which of the following diseases may produce a burning sensation? (A) Burning mouth syndrome (B) Xerostomia (C) Vitamin deficiencies (D) All of the above
<b>答案(D)</b>	出處：p.40, Differential Diagnosis of Oral and Maxillofacial Lesions, 5 <sup>th</sup> edition
<b>題號</b>	<b>題目</b>
<b>2</b>	Which of the followings is included in generalized mucosities and vesiculobullous diseases? (A) <i>Behcet's</i> syndrome (B) Erosive lichen planus (C) Erythema multiforme (D) All of the above
<b>答案(D)</b>	出處：p.171, Differential Diagnosis of Oral and Maxillofacial Lesions, 5 <sup>th</sup> edition