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內文:

Gingival Hyperplasia

- Gingival hyperplasia or gingival overgrowth is characterized by an accumulation of extracellular matrix within the gingival connective tissue, particularly the collagenous component, with various degrees of chronic inflammation.
- Phenytoin, cyclosporine-A, calcium channel blockers, and oral contraceptives are main causative agents of drug-induced gingival hyperplasia.
- The prevalence rate of this disorder has been reported to vary: 10% to 50% for phenytoin; 8% to 70% for cyclosporine-A; and 0.5% to 83% for nifedipine
- The growth starts as a painless, beadlike enlargement of the interdental papilla and extends to the facial and lingual gingival margins.
  The enlargement is usually generalized throughout the mouth but is more severe in The maxillary and mandibular anterior regions.
- Plaque removal and maintaining good oral hygiene may provide benefits in terms of rapid recovery and limitation of the severity of the lesion but the lesion does not completely resolve. It is hypothesized fibroblasts in non-inflamed gingiva are less active, or even quiescent, and do not respond to circulating systemic drugs. In contrast, fibroblasts within inflamed tissue are in an active state and responsive to drug therapy as a result of inflammatory mediators and the endogenous growth factors.
- The incidence of phenytoin-induced gingival overgrowth is approximately 50%, but it is higher in both teenagers and institutionalized epileptics.
- Gingival overgrowth usually becomes apparent during the first three months after starting phenytoin and is more rapid in the first year.
  Nifedipine, the most commonly used calcium channel blocker, induces gingival enlargement in 20% of the cases.[65] Amlodipine, diltiazem, felodipine, nitrendipine, and verapamil also induce gingival overgrowth.
- It has been shown nifedipine-induced gingival hyperplasia accompanies submandibular gland dysfunction evidenced by the reduction of salivary flow rate and concentrations of EGF calcium, and total protein.
- There is also evidence nifedipine inhibits both the adherence and lipoploysaccharide-stimulated macrophageinduced death of fibroblasts which results in gingival overgrowth. Nifedipine is frequently prescribed to organ transplant patients to reduce the nephrotoxic effects of cyclosporine and, thus, an additive effect on the gingival tissues is usually observed.

- The incidence of gingival overgrowth by oral contraceptives is not rare and resolves when the drug is withdrawn. There is evidence the accumulation of metabolic products of the naturally occurring sex hormones in gingiva is an important factor in the pathogenesis of chronic gingivitis. The prevalence and percentage of incidence is uncertain. Maintenance of adequate plaque control is important for gingival health during the administration of oral contraceptives.
- The treatment options for drug-induced gingival enlargement should be based on the medication being used and the clinical presentation of each particular case. Consideration should be given first to the possibility of discontinuing the drug or of changing medication.
- Drug substitution is a second alternative. There is also preliminary evidence the antibiotic azithromycin may aid in decreasing the severity of cyclosporin-induced gingival enlargement. If any drug substitution is attempted, it is important to allow six-12 months to elapse between discontinuation of the offending drug and the possible resolution of gingival enlargement before a decision to implement surgical treatment is made.
- The clinician should also emphasize plaque control as the first step in the treatment of druginduced gingival enlargement.
- Although the exact role played by bacterial plaque in druginduced gingival enlargement is unclear, there is evidence good oral hygiene and frequent professional removal of plaque decreases the degree of the gingival enlargement and improves overall gingival health.
- If gingival enlargement persists, despite drug substitution attempts and good plaque control, it needs to be treated by periodontal surgery

Table 14. Drugs with potential to cause gingival hyperplasia.[3,5,22]

• Bepridil • Calcium channel blockers • Cannabis • Cotrimoxazole • Cyclosporine • Erythromycin • Ethosuximide	• Ethotoin • Flunarizine • Ketoconazole • Lamotrigine • Lithium • Mephenytoin • Phenytoin	• Phenobarbital • Primidone • Sertraline • Sodium valproate • Topiramate • Vigabatrin

Salivary Glands

- The most important functions of saliva are to facilitate digestion by lubricating and initiating the chemical processing of food and to protect the mucosa and teeth.
- Saliva is protective through a cleansing action as well as through the antimicrobial action of various salivary components such as mucin, histatins, lysozyme, and lactoferrin and through the function of specific antibodies to a range of microorganisms the host has encountered.
- Salivary gland function can be affected by a variety of drugs that can produce xerostomia or ptyalism.
- Drugs recognized as causes of reduced salivation include mainly those with cytotoxic,

anticholinergic, sympathomimetic, or diuretic activity.[7]

- Common oral manifestations resulting from decreased salivary flow include increased dental caries, fungal infections, bacterial infections, aphthous lesions, and dysphagia.
- Pliocarpine and bethanechol have been suggested to be of potential use in the management of drug-induced xerostomia.
- Sialorrhoea or ptyalism, the condition of increased salivary flow, is uncommon. Salivary hypersecretion is usually caused by physiological factors such as menstruation or early pregnancy, local factors such as teething, oral inflammatory lesions, food, medications, or by nasogastric intubation.
- Major medication groups that are clearly associated with sialorrhoea are antipsychotics, particularly clozapine, and direct and indirect cholinergic agonists that are used to treat dementia of the Alzheimer type and myasthenia gravis.

Table 15. Drugs with the potential to affect salivary glands.[29,52,76,81-104]

Drugs and chemicals implicated in xerostomia		
• Alizapride • Alpha 1 antagonists (e.g. terazosin, prazosin, alfuzosin) • Alpha 2 antagonists (e.g. clonidine, lofexidine) • Ambroxol • Amphetamines • Antihistamines • Anti-HIV protease inhibitors • Antimigrain agents • Antineoplastics • Antiparkinson drugs • Atropine • Benzodiazepines • Beta blockers (e.g. atenolol, propranolol) • Belladonna alkaloids • Botulinum toxin type-A • Bupropion • Cadmium • Calcium channel blockers • Ciprofloxacin • Clidinium • Clozapine • Cyclobezaprine • Cyclopentolate • Cyclosporine • Cytokines • Dexmedetomidine • Ephedrine • Fenfluramine • Gentamycin	• Glycopyrolate • Guanabenz • Guanfacine • Hyoscine • Insulin • Ipratropium • Isotretinoin • Ketanserin • Ketotifen • L-dopa • Lead • Lithium • Lubiprostone • Mazindol • Methdilazine • Modafinil • Molindone • Monoamine oxidase inhibitors • Nabilone • Nefazodone • Nefopam • Nicotine • Nitric oxide inhibitors • Ofloxacin • Olanzapine • Ondansetron • Opioids • Orphenadrine • Oxybutynin • Paliperidone • Paricalcitol	• Peginterferon alfa-2a • Phenothiazines • Phenylpropanolamine • posaconazole • Pregabalin • Propantheline • Proton pump inhibitors (e.g. omeprazole) • Radioiodine • Rasagiline • Risedronate • Rotigotine • Selective serotonin reuptake inhibitors • Solifenacin • Sotalol • Spiramycin • Tadalafil • Terodiline • Thiabendazole • thioridazine • Tiamenidine • Tizanidine • Trazodone • Tricyclic antidepressants • Tropicamide • Venlafaxine • Vereniciline • Vigabatrin • Vorinostat • Zuclopenthixol
Drugs that can cause sialorrhea		
• Alprazolam • Ambroxol • Amiodarone • Bethanechol • Buspirone • Clozapine • Desflurane • Diazoxide • Digoxin • Edrophonium • Galantamine • Gentamycin • Guanethidine • Imipenem/Cilastatin	• Iodides Kanamycin • Ketamine • Lamotrigine • Levodopa • Lithium • Mianserin • Mefenamic Acid • Mercurial salts • Modafinil • Neostigmine • Nifedipine • Niridazole • Nitrazepam • Olanzapine	• Organophosphates • Pentoxifylline • Physostigmine • Pilocarpine • Risperidone • Rivastigmine • Sildenafil Succinylcholine • Tacrine • Theophylline • Tobramycin • Venlafaxine • Zaleplon • Zonisamide
Drugs that have potential to cause swelling and/or pain in salivary glands		
• Bretylium • Catecholamine inhalation • Chlorhexidine • Cimetidine • Clonidine • Clozapine • Deoxycycline	• Famotidine • Iodine • Methyldopa • Naproxen • Nifedipine • Nitrofurantoin	• Phenytoin • Ranitidine • Ritodrine • Sulfonamides • Trimipramine • Warfarin

Effects on Dental Structure

- Enamel fluorosis is a hypomineralization of enamel characterized by greater surface and subsurface porosity than in normal enamel as a result of excess fluoride intake during the period of enamel formation.
- Preventive management of dental fluorosis includes de-fluoridation of drinking water in endemic areas, cautious use of fluoride supplements, and supervision of the use of fluoride toothpaste by children below five years of age.
- Pre-natal exposure to anticonvulsants has been shown to cause a significant increase in mesiodistal crown dimensions of the posterior maxillary teeth-specifically, primary molars and their permanent premolar successors, as well as permanent molars
- Hypodontia and disturbance in root formation were also observed following anticonvulsant administration.

Table 16. Agents with potential to affect dental structures.

Agent	Example	Possible Damage
Sugar-containing oral (liquid) medication	Various liquid medications	Dental caries
Drugs that result in decreased salivary secretion (xerostomia)	See Table 13	Dental caries
Drugs with a pH low enough to cause tooth erosion	Aspirin, anti-asthmatic drugs	Dental erosion
Drugs that may increase susceptibility to gastro-esophageal reflux disease	Theophylline, anticholinergics, progesterone, calcium channel blockers, anti-asthmatics	Dental erosion
Drugs used for internal tooth bleaching	Hydrogen peroxide and sodium perborate	Cervical root resorption
antineoplastic drugs		Abnormal dental development
Anticonvulsants	Phenytoin	Changes in tooth size, hypodontia, disturbance in root formation
Biphosphonates	Zoledronic acid, pamidronate, alendronate, clodronate	Osteonecrosis of jaws
Amlexanox, Niacin, Silver		Dental pain
Fluoride		Dental fluorosis

Oral Motor Disorders

- These medications and illegal drugs produce a motor response that is classified better as an unspecified extrapyramidal syndrome (EPS) reaction. EPS responses typically have three presentations: dystonia, akathisia, and parkinsonism
- Dystonic reactions consist of involuntary, tonic contractions of skeletal muscles

- Akathisia reactions occur as a subjective experience of motor restlessness. Patients may complain of an inability to sit or stand still or a compulsion to pace or cross and uncross their legs
- Parkinsonian reactions manifest themselves as tremor, rigidity, and akinesia, which shows as a slowness in initiating motor tasks and fatigue when performing activities that require repetitive movements (bradykinesia)
- Most of the literature has focused on the more severe acute dystonic EPS reactions that occur with use of antipsychotic medications. In addition to the antipsychotics, several antiemetics with dopamine receptor–blocking properties have been associated with tardive dystonia.

- The most commonly reported offending agents other than neuroleptics are the selective serotonin reuptake inhibitors (SSRIs) and the stimulant medications and illegal drugs SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram) are reported to produce the side effect of increased clenching and bruxism.
- Fortunately, acute dystonic reactions secondary to drugs disappear upon discontinuation of the medication
- If the suspected medication cannot be stopped or if the motor hyperactivity is severe diphenhydramine or benztropine are administered intravenously or intramuscularly to treat the motor hyperactivity. It should be noted amantadine and intravenous diazepam have been shown to be effective for recurrent neuroleptic-induced dystonic reactions.

Taste Disorders

- The alternation in taste may be simply a blunting or decreased sensitivity in taste perception (hypogeusia), a total loss of the ability to taste (ageusia), or a distortion in perception of the correct taste of a substance, for example, sour for sweet (dysgeusia)
- Sulfhydryl compounds are a common cause of taste disturbance
- Penicillamine causes partial or total loss of taste in many patients In patients treated for Wilson's disease, the frequency is much lower. Loss of taste has been found to be dose related. Taste disturbance is reversible within a period of eight to ten weeks, whether or not penicillamine is discontinued.
- Taste disturbances tend to be selflimiting and reversible in two to three months even if the drug is continued.
- Other drugs, especially those used for gastrointestinal disorders such as tripotassium dicitrato bismuthate chelate, clarithromycin, lansoperazole, anti-HIV protease inhibitors, terbinafine, intravenous pentamidine, and isotretinoin may cause some degree of loss of taste or altered taste.

Halitosis

- Halitosis or oral malodor is offensive breath resulting from poor oral hygiene, dental or oral infections, ingestion of certain foods, use of tobacco, and some systemic diseases and

medications.[5]

Table 20. Drugs that can induce halitosis.[25,122]

- Chloral hydrate
- Cytotxic drugs
- Dimethyl sulphoxide
- Disulfiram
- Nitrites and nitrates
- Succimer

Oral Infections

- Subjective complaints of localized oral burning are sometimes empirically treated for candidiasis.
- Objective assays in the diagnosis of oral candidiasis include exfoliative cytology, imprint culture, swab culture, salivary assays, and mucosal biopsy. Topical and systemic antifungal agents are used more frequently by dentists to treat oral fungal infections.

Table 21. Drugs with potential to cause oral candidiasis.[5,29]

- Alglucosidase alfa
- Antibiotics
- Antineoplastics
- Arformoterol
- Atovaquone
- Cephalosporins
- Ciprofloxacin
- Clarithromycin
- Conivaptan
- Corticosteroids
- Griseofulvin
- Immunosuppressives
- Mesalamine
- Olanzapine
- Omeprazole
- Oral contraceptives
- Riluzole

Alveolar Osteitis

- Alveolar osteitis, commonly referred to as “dry socket”, is by far the most common complication following dental extraction and has been defined as an inflammation of the alveolus.
- The use of oral contraceptives has been associated with a significant increase in the frequency of dry sockets after removal of impacted lower third molars
- Dry socket is clinically recognizable by the existence of a naked alveolus without the presence of a sanguine clot revealing the exposed bony walls and separation of gingival borders
- Dry socket typically appears on the second or third day following an extraction and usually lasts about ten or 15 days regardless of whether it is treated or not
- the global tendency is to carry out analgesic symptomatic treatment, accompanied by antinflamatory treatment and antibiotics. Some authors advise the placement of antiseptic intra-alveolar pastes

Angioedema

- Angioedema is a sudden occurrence of subcutaneous or submucosal swelling
- It is well known and in cases where the pharynx or larynx are involved it can be a potentially life-threatening condition
- The majority of cases of angioedema are due to allergic reactions. Some drugs like penicillin and sulfa drugs can cause allergic angioedema. Beside the well-known forms of allergic angioedema, many forms of non-allergic angioedema are known
- Some drugs have the potential to induce nonallergic angioedema; among them the ACEIs arethe most important. Angioedema is an established and potentially life threatening side effect of ACEIs.
- The incidence of ACEI-induced angioedema is 0.4–0.7%. The mortality worldwide is 0.1% of these cases
- A variety of non-steroidal anti-inflammatory drugs (NSAIDs) can cause angioedema. Aspirin is the most common and the reaction is called pseudoallergic angioedema. Only cyclooxygenase (COX)-1 inhibitors cause pseudoallergic angioedema,
- Acetaminophen is generally tolerated even by patients sensitive to aspirin, most likely because of very weak COX-1 inhibition
- Angioedema is usually treated by a conservative clinical approach using artificial ventilation, glucocorticoids, and antihistamines.

Table 22. Drugs that can cause angioedema.[5,127,129]

• ACEIs • Adrenomimetic bronchodilators • Altepase • Amlodipine • Angiotensin II receptor agonists • Estrogens • Fluoxetin	• Intravenous clindamycin • Ketoconazole • Laronidase • Lepirudin • Mianserin • Midazolam	• NSAIDs • Penicillin • Rituximab • Sulfa drugs • Tacrine • Tacrolimus

Cheilitis

- Cheilitis is an abnormal condition of the lips characterized by inflammation and cracking of the skin. This is usually associated with fungal infections and frequently occurs with druginduced

xerostomia.

Table 23. Drugs with potential to cause cheilitis.[5,29]

• Atorvastatin • Busulfan • Clofazimine • Clomipramine • Cyanocobalamin • Gold compounds • Indinavir	• Isotretinoin • Methyldopa • Panitumumab • Prochlorprazine • Psoralens • Ritonavir	• Saquinavir • Simvastatin • Streptomycin • Sulfasalazine • Tetracycline • Vitamin A

Conclusion

Since most drug reactions occur within one to two weeks following initiation of therapy, reactions seen after two weeks are less likely to be due to medication use. Some reactions are dependent on dosage or cumulative toxicity. The majority of drug-induced oral reactions are moderate in severity In most cases, the oral reaction will be resolved by symptomatic treatment Reactions after such a re-challenge may be more severe and, therefore, a re-challenge should not be performed without medical supervision.

題號 1	題目
	下列那種藥物不會引起 gingival hyperplasia? (A)calcium channel blocker (B)phenytoin (C)erythromycin (D)atopine
答案(D)	出處: **Oral & Maxillofacial Pathology (2nd edition),P200**
題號 2	題目
	Alveolar osteitis 最常發生的位置? (A)mandibular 1st molar (B)maxillary 1st molar (C)mandibular 3rd molar (D)maxillary 3rd molar
答案(C)	出處: **Oral & Maxillofacial Pathology (2nd edition),P305**