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Drug-Induced Gingival Hyperplasia

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AUTHOR INFORMATION

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Author: [Piamkamon Vacharotayangul, DDS, PhD](#), Lecturer, Division of Oral Medicine, Department of Oral Surgery and Oral Medicine, Faculty of Medicine, Sri Nakharinwirot University School of Dentistry, Bangkok, Thailand

Coauthor(s): [Francina Lozada-Nur, DDS, MS, MPH](#), Department of Orofacial Sciences, Professor, Program Director in Advanced Program in Oral Medicine, University of California at San Francisco; Associate Clinical Professor, [Department of Dermatology, Stanford University](#)

Piamkamon Vacharotayangul, DDS, PhD, is a member of the following medical societies: [American Academy of Oral Medicine](#)

Editor(s): **Franklin Flowers, MD**, Chief, Division of Dermatology, Professor, Department of Medicine and Otolaryngology, University of Florida College of Medicine; **David F Butler, MD**, Professor, Texas A&M University College of Medicine; Director, Division of Dermatology, Scott and White Clinic; **Drore Eisen, MD, DDS**, Consulting Staff, Department of Dermatology, Dermatology Research Associates of Cincinnati; **Glen H Crawford, MD**, Assistant Clinical Professor, Department of Dermatology, University of Pennsylvania School of Medicine; Chief, Division of Dermatology, The Pennsylvania Hospital; and **William D James, MD**, Paul R Gross Professor of Dermatology, University of Pennsylvania School of Medicine; Vice-Chair, Program Director, Department of Dermatology, University of Pennsylvania Health System

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INTRODUCTION

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Background: Gingival overgrowth (GO), also known as gingival hyperplasia secondary to drugs, was first reported in the dental literature in the early 1960s in institutionalized epileptic children who were receiving therapy with phenytoin (Dilantin) for the treatment of seizures. Recently, cyclosporine (a potent immunosuppressant widely used since the early 1980s in organ transplant recipients and for psoriasis) and numerous calcium channel blocker agents (especially nifedipine) have been associated with GO. Nifedipine appears to have an additive effect when used together with cyclosporine in transplant recipients with hypertension.

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Because not all patients on phenytoin, cyclosporine, or calcium antagonists develop GO, identifying patients at risk is important in order to take the necessary measures to minimize the onset and severity of this condition.

Currently, the etiology of drug-induced GO is not entirely understood but is clearly multifactorial. One of the main reasons for this is that clinical and epidemiologic studies on the role of drugs in GO are retrospective.

Some of the risk factors known to contribute to GO include the presence of gingival inflammation (gingivitis due to poor oral hygiene), presence of dental plaque that may provide a reservoir for the accumulation of phenytoin or cyclosporine, the depth of the periodontal pocket on probing, and the dose and duration of cyclosporine therapy.

Other intrinsic risk factors include the susceptibility of some subpopulations of fibroblasts and keratinocytes to phenytoin, cyclosporine, or nifedipine, and the number of Langerhans cells present in oral epithelium. The latter appears to be related to the presence of inflammation and dental plaque.

Because most of the studies reported so far observed patients who had GO at the time of the study, it is quite difficult to determine the true effect of the medication independent of cofactors (ie, severity of the underlying disease, oral health status prior to the onset of GO [premature tooth loss, periodontal disease, routine oral hygiene], socioeconomic status, education); however, it is clear that the status of oral/dental health prior to onset of GO combined with medication are involved in the onset of this condition.

Pathophysiology: Several studies have shown that the interaction of phenytoin, cyclosporine, and nifedipine with epithelial keratinocytes, fibroblasts, and collagen can lead to an overgrowth of gingival tissue in susceptible individuals. Phenytoin has been shown to induce GO by its interaction with a subpopulation of sensitive fibroblasts. Cyclosporine has been suggested to affect the metabolic function of fibroblast (eg, collagen synthesis, breakdown), whereas nifedipine, which potentiates the effect of cyclosporine, reduces protein synthesis of fibroblasts. A review of existing literature shows that a cofactor clearly is needed to induce GO.

Frequency:

- **In the US:** GO is a rare condition, and no population-based or epidemiologic studies exist in the United States. Incidence rates are reported from case-series studies. The prevalence of phenytoin-induced GO is estimated at 15-50% in patients taking the medication. The prevalence for cyclosporine transplant recipient patients is 27%; however, these numbers should be interpreted with caution. The incidence of gingival hyperplasia has been reported as 10-20% in patients treated with calcium antagonists in the general population. Clinicians should look at the population represented within each particular study (ie, young persons with epilepsy, recipients of transplants).
- **Internationally:** No incidence or prevalence epidemiologic data is available on GO worldwide. In India, 57% of epileptic children aged 8-13 years who were undergoing phenytoin monotherapy developed GO within 6 months of treatment.

Mortality/Morbidity: No mortality is associated with gingival enlargement. Morbidity can be severe in some cases because of gross overgrowth of gingival tissue, which can lead to gingival bleeding, pain, teeth displacement, and periodontal disease.

Race: No racial predilection exists for the onset of drug-induced GO.

Sex: No sexual predilection exists for drug-induced GO, although in one study, males were 3 times more likely than females to develop GO with calcium antagonists.

Age: No age predilection exists for the onset of drug-induced GO; however, phenytoin-induced GO appears to be more frequent in young patients with epilepsy. Most likely, this may be related to the age of the population, the nature of the disease, and poor oral hygiene.

CLINICAL

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History: The onset of drug-induced GO in susceptible individuals is insidious. GO is asymptomatic, except in the presence of poor oral hygiene and dental plaque because patients may develop bleeding with tender and swollen gums. Patients with malpositioned teeth, periodontal disease, and poor oral hygiene are at risk of developing GO. Severity varies depending on the oral/dental health prior to the beginning of therapy; however, not all patients with poor oral hygiene develop drug-induced GO.

- Phenytoin-induced GO
 - This is more likely to occur in patients with gingivitis and dental plaque.
 - Increased dental plaque has been suggested to induce local inflammation and to serve as a reservoir for phenytoin.
- Cyclosporine-induced GO
 - In susceptible patients (ie, presence of dental plaque, swollen gums, high dose of cyclosporine), GO may

develop by the third month of therapy.

- Patients with poor oral hygiene and displaced teeth tend to develop bleeding gums upon probing.
- Aggressive plaque control and routine oral hygiene help in maintaining gums but may not prevent the onset of GO in susceptible individuals.
- Cyclosporine-induced GO is reversible once therapy is discontinued or when the dose is reduced.
- Cyclosporine- and nifedipine-induced GO: Nifedipine potentiates the adverse effect (ie, GO) of cyclosporine.
- Calcium antagonist-induced GO
 - Oral hygiene plays a decisive role in the development of gingival enlargement.
 - Substantial evidence in the dental literature indicates that gingival enlargement can be controlled successfully, even under the continuous administration of calcium antagonists, by meticulous professional and individual oral hygiene.

Physical:

- Gingival enlargement occurs primarily on the labial gingival mucosa and in between the teeth (interdental papillae area).
- GO is more pronounced on the labial aspect of the maxillary gingiva and in the interdental papillae.

Causes: Potential risk factors for drug-induced GO include the following:

- Poor oral hygiene
- Periodontal disease
- Periodontal pocket depth
- Gingival inflammation
- Degree of dental plaque
- Duration and dose of cyclosporine

DIFFERENTIALS

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Other Problems to be Considered:

Leukemia (bleeding gums)
Pyogenic granuloma
Pregnancy tumor
Warts

WORKUP

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Lab Studies:

- CBC count is indicated in patients with severe gum bleeding to rule out anemia and leukemia.

Imaging Studies:

- Periapical (full mouth series) or Panorex (panoramic view) radiographs are indicated prior to treatment to evaluate the status of the periodontal tissue or any compromised teeth.

Other Tests:

- Culture is recommended to rule out oral candidiasis.

Procedures:

- Tissue biopsy may be indicated if GO has an unusual clinical presentation or if the patient is not on a medication known to induce GO.
- Periodontal examination is necessary to evaluate for the presence of periodontal disease.

- Dental hygiene is required to remove dental plaque.
- Root planing may be indicated.
- Dental extraction of periodontically compromised teeth is indicated if those teeth may interfere with subsequent medical treatment. It also may be considered if the patient cannot perform prophylactic dental care (eg, young epileptic patient).

Histologic Findings: Histologic changes are similar in GO that is caused by either phenytoin or cyclosporine. The term gingival hyperplasia is inappropriate because enlargement does not result from an increase in the number of cells but rather an increase in extracellular tissue volume.

A highly vascular connective tissue occurs histologically with focal accumulation of inflammatory cells, primarily plasma cells. The overlying epithelium is of variable thickness, irregular, and multilayered. Acanthosis and parakeratosis with pseudoepitheliomatous proliferation have been reported.

Immunohistologic studies have demonstrated an increase in the number of Langerhans cells within the epithelium and adjacent to inflamed sites.

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Medical Care: For dental care, refer patients to a general dentist or oral medicine specialist prior to any organ transplant and before starting treatment with phenytoin, cyclosporine, or any calcium channel blocker known to induce GO.

Surgical Care: Gingivectomy with carbon dioxide or YAG laser is recommended for patients who have moderate-to-severe gingival enlargement that does not resolve when the dose is reduced, proper oral hygiene is maintained, or after a short course of antibiotics.

Consultations:

- For evaluation and treatment planning, refer patients to a dental practitioner and an oral medicine specialist familiar with the oral care of medically complex patients.
- An oral medicine specialist and a periodontist should monitor patients with GO for as long as they receive therapy with cyclosporine, phenytoin, or calcium channel blockers to evaluate and treat oral complications from medical therapy.

Diet: No diet restrictions are recommended for patients with GO other than minimizing the consumption of sweets, starch, soft drinks, and simple carbohydrates.

Activity: No activity restrictions are reported.


The ABCs of Antithrombotic Therapy in Peripheral Arterial Disease

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Peripheral arterial disease (PAD) affects more than 12 million Americans. PAD is symptomatic as intermittent claudication in 2–3% of men and 1–2 % of women older than 60 years. The prevalence of asymptomatic PAD, generally shown by a reduced ankle-brachial index (ABI), is 3–4 times greater. PAD is also a significant cause of hospital admission and is an important predictor of heart attack, stroke, and cardiovascular death. PAD can disrupt blood flow to arteries outside of the heart; over time, the lack of blood flow can lead to kidney failure, amputation of legs and arms, or severely high blood pressure. This CME activity is designed to examine PAD risk factors and treatment strategies. (Approved for *AMA PRA Category 1 Credit™*.)

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Drug Category: *Antibiotics* -- Empiric antimicrobial therapy must be comprehensive and should cover all likely pathogens in the context of the clinical setting.

Drug Name	Azithromycin (Zithromax) -- Used to treat mild-to-moderate oral microbial infections. Macrolide antibiotic that acts by suppressing protein synthesis of gram-positive and gram-negative aerobes. Take 1-2 h after meals.
Adult Dose	Day 1: 500 mg PO Days 2-5: 250 mg PO qd
Pediatric Dose	>6 months Day 1: 10 mg/kg PO once; not to exceed 500 mg/d Days 2-5: 5 mg/kg PO qd; not to exceed 250 mg/d
Contraindications	Documented hypersensitivity; hepatic impairment; do not administer with pimozone
Interactions	May increase toxicity of theophylline, warfarin, and digoxin; effects are reduced with coadministration of aluminum and/or magnesium antacids; nephrotoxicity and neurotoxicity may occur when coadministered with cyclosporine
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Site reactions can occur with IV route; bacterial or fungal overgrowth may result with prolonged antibiotic use; may increase hepatic enzymes and cholestatic jaundice; caution in patients with impaired hepatic function, prolonged QT intervals, or pneumonia; caution in patients who are hospitalized, geriatric, or debilitated

Drug Category: *Mouthwash antiseptics* -- Antiseptic agent for oral bacterial and fungal infections.

Drug Name	Chlorhexidine gluconate (Peridex) -- Effective, safe, and reliable mouthwash antiseptic. Polybiguanide with bactericidal activity; usually is supplied as a gluconate salt. At physiologic pH, the salt dissociates to a cation that binds to bacterial cell walls.
Adult Dose	15 mL rinse and expectorate/spit bid after thoroughly brushing teeth to prevent staining
Pediatric Dose	5-10 mL rinse and expectorate/spit bid after thoroughly brushing teeth to prevent staining
Contraindications	Documented hypersensitivity; avoid in the presence of any oral ulcers or if patient presents with mucositis secondary to radiation or chemotherapy
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Irritation if open ulcers are seen in the mouth; dental deposits, staining of teeth, taste changes, and parotitis have been reported
Drug Name	Lysozyme, lactoferrin, glucose oxidase, lactoperoxidase (Biotene) -- Alcohol-free mouthwash antiseptic.
Adult Dose	Rinse mouth bid/tid pc
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	None reported

FOLLOW-UP

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Further Outpatient Care:

- To monitor for GO-associated oral complications (eg, bleeding gums, poor oral hygiene, gingivitis, oral candidiasis), oral medicine specialists should provide follow-up care twice a year for patients taking drugs known to induce GO.
- Dental hygiene is recommended every 3 months to control dental plaque.
- Patients should practice thorough oral hygiene twice a day (ie, before breakfast, before going to bed) and rinse mouth with plain water after each meal.

In/Out Patient Meds:

- Chlorhexidine 12% once before going to bed or Biotene mouthwash after meals is recommended for those patients known to be at risk for gingivitis.

Deterrence/Prevention:

- Ensure healthy periodontal tissue prior to any organ transplantation or the use of phenytoin or calcium channel blocker.
- Consider alternative drugs (ie, mycophenolate [CellCept], or tacrolimus [Prograf] in organ transplant recipients, verapamil in place of calcium channel blockers) for patients at high risk. One study showed that in a case of pediatric renal transplantation, GO was improved after switching from cyclosporine A to tacrolimus.
- Use lower doses of cyclosporine.
- Educate patients about the importance of good oral hygiene and routine dental care, not only to minimize GO but also to reduce risk of systemic complications, including organ rejection.

Complications:

- Severe GO in patients with poor oral health can lead to early tooth loss.
- Chlorhexidine 12% mouthwash might cause teeth staining; however, brushing teeth prior to rinsing out with chlorhexidine can prevent it. The stain can be removed by routine oral prophylaxis.

Prognosis:

- The prognosis is better if patients maintain regular oral hygiene and plaque control.

Patient Education:

- Inform patients of the risk of developing gingival enlargement secondary to therapy and the role of oral health in minimizing complications from therapy.
- Advise patients to see a pedodontist, a periodontist, and an oral medicine dentist for a baseline evaluation; full mouth x-ray films; tooth extractions, if needed; and dental hygiene before transplant or the use of any drug known to induce GO.
- For excellent patient education resources, visit eMedicine's [Teeth and Mouth Center](#). Also, see eMedicine's patient education articles [Gingivitis](#) and [When to Visit the Dentist](#).

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- Failure to perform appropriate diagnostic procedures (ie, periodontal evaluation, full mouth x-ray film, routine histology)
- Failure to appropriately identify and monitor patients at risk for the development of gingival overgrowth secondary to systemic therapy known to induce gingival overgrowth (ie, regular oral hygiene, frequent visits to dental professional)

Special Concerns:

- Emphasize the importance of good oral hygiene and routine dental care.
- In a patient who is pregnant, rule out pregnancy tumor/pyogenic granuloma.
- Refer all patients, regardless of sex and age, to their dentists prior to therapy with medications known to induce GO.

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Caption: Picture 1. Swelling of the gingival mucosa around the right lower canine and multiple areas of erythema, erosions, and bleeding throughout the upper gingival mucosa.



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Picture Type: Photo

Caption: Picture 2. Enlarged upper and lower gingival mucosa in a partially edentulous patient. Notice how the overgrown tissue tends to engulf the teeth. Poor oral hygiene and poor dentition are the most likely contributing factors in this patient receiving immunosuppressive therapy.



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Picture Type: Photo

Caption: Picture 3. A palatal view of same patient as in Image 2. Notice the severity of the gingival enlargement. If left untreated, patients develop severe periodontal disease and lose teeth.



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Picture Type: Photo

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