

Faculdade de Medicina Dentária da Universidade do Porto



USE OF TOPICAL CORTICOSTEROIDS IN ORAL PATHOLOGY - A REVIEW

Dissertação de artigo de revisão bibliográfica apresentada à Faculdade de Medicina Dentária da Universidade do Porto, de acordo com o regulamento da Unidade Curricular da “Monografia de investigação/Relatório de atividade clínica” do Mestrado Integrado em Medicina Dentária.

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Index

Introduction	1
Material and methods	2
Glucocorticoids	3
The inflammatory response.....	6
Glucocorticoids’ anti-inflammatory activity.....	6
Indications.....	9
Side effects and contraindications	10
Interactions with other drugs	12
Use in Dental Practice.....	13
Topic glucocorticoids.....	13
Oral Pathology.....	16
Oral Lichen Planus.....	16
Treatment	17
Pemphigus.....	19
Treatment	21
Bullous pemphigoid	21
Treatment	23
Recurrent aphthous stomatitis.....	24
Treatment	25
Conclusion.....	27
Bibliography.....	28
APPENDICES.....	32

Figures Index

Figure 1: Transverse and microscopic sections of the adrenal cortex. Each one synthesizes a specific class of steroid hormones: glomerulosa zone secretes essentially, the mineralocorticoid aldosterone, fasciculada zone broadly synthesizes the glucocorticoid cortisol, and reticular zone broadly produces adrogens	4
Figure 2: Mechanism of cortisol secretion and negative feedback regulation. (Adapted from Daniel E.Becker, 2013)	5
Figure 3:Schematic illustration of the glucocorticoids anti-inflammatory effects	8
Figure 4: Presence of oral lichen planus on the oral mucosa (right cheek). Courtesy of Prof. Dr. Otília Lopes	17
Figure 5: Presence of erosive oral lichen planus on the oral mucosa (left cheek). Courtesy of Prof. Dr. Otília Lopes	17
Figure 6: Diagram representing the process of acantholysis resulting from the attack of the auto-antibodies to the antigens of keratinocytes.....	20
Figure 7: Diagram explaining the process of auto-immune activation that leads to the blister formation in Bullous pemphigoid.....	22
Figure 8: Presence of bullous pemphigoid lesions on the oral mucosa. Courtesy of Prof. Dr. Otília Lopes	23
Figure 9: Presence of major ulcer on the lips. Courtesy of Prof. Dr. Otília Lopes	25

Table Index

Table I: Resume of the glucocorticoid’s indications based on their properties.....	9
Table II:Summary of principal characteristics of the most common topical glucocorticoids prescribed in oral pathology	15
Table III:Evidence basis for the value of topical glucocorticoids in the treatment of Oral Lichen Planus (Adapted from Al-Hashimi et al, 2007)	18
Table IV:Principal clinical characteristics of the 3 forms of recurrent aphthous stomatitis (RAS) (Adapted from Zuzzana S. et al, 2014)	24
Table V:Indications of topical glucocorticoids in the treatment of Recurrent Aphthous Stomatitis	26

Abbreviation Index

11 β -HSD1 - 11 β -hydroxysteroid dehydrogenases type 1

11 β -HSD2 - 11 β -hydroxysteroid dehydrogenases type 2

ACTH - adrenocorticotrophic hormone

Anx-1- annexin-1

COX-2 - Ciclo-oxigenase-2

CRH- corticotrophin-releasing hormone

ERKs - extracellular signal-regulated kinases

GC – glucocorticoid

GR - glucocorticoid receptor

GILZ - glucocorticoid-induced leucine zipper

GREs - palindromic glucocorticoid response elements

HIV - Human Immunodeficiency Virus

HPA – hypothalamic-pituitary-adrenal

IgE – immunoglobulin E

IL - interleukin

JNKs - c-Jun NH₂-terminal kinases

MAPKs - Mitogen – activated protein kinases

MPK-1 - MAPK phosphatase-1

NF- κ B - nuclear factor κ B

OLP – Oral Lichen Planus

p38s - p38 isoforms

RAS – recurrent aphthous stomatitis

TNF- α – tumour necrosis factor-alpha

Abstract

Introduction: Corticosteroids are steroid hormones synthesized and secreted by the adrenal gland that modulate a wide range of physiological processes, including stress response, immune-inflammatory response, carbohydrate and protein catabolism, blood electrolyte levels, and behaviour. Topic corticosteroids are more frequently used in the dental practice, generally focusing on the symptomatic management of oral mucosa conditions.

Objective: This work is set on the clinical use of topical corticosteroids in dental practice, namely for the management of oral mucosal conditions, embracing the indications, contraindications, advantages and disadvantages of their use, as well as the different forms of administration (use of adhesive ointments, gels, intra-lesion injections, customized tray) and therapeutic regimens, for the optimizations of the clinical output.

Material and Methods: The search for relevant references and articles was conducted in the PubMed and Scopus databases. The following combination of keywords was used: topical corticosteroids, corticosteroids, systemic corticosteroids, glucocorticoids, topical glucocorticoids, systemic glucocorticoids, treatment guidelines, pregnancy, oral pathology, dental medicine, oral mucosa, oral lichen planus, pemphigous, pemphigoid, recurrent aphthous stomatitis. Mainly review articles, research articles, clinical trials and case reports were selected, which publication date was comprehended between 2005 and 2016. Only papers in Portuguese or English, with access to the full text were chosen, according to their relevance to the theme to describe. Following, each article was evaluated for inclusion by its content analysis.

Conclusion: Guidelines for treatment / maintenance of distinct conditions with topical corticosteroid therapy were found available, especially regarding oral lichen plan and recurrent aphthous stomatitis conditions. However, less is known regarding therapeutic management of pemphigus vulgaris or bullous pemphigoid, since the majority of the literature refers to dermatology guidelines. As absorption by the skin is not as the one in oral mucosa, more studies should be conducted in these areas in order to disclose therapeutic guidelines adequately focused on the oral management of these conditions.

Resumo

Introdução: Os corticosteróides são hormonas esteróides sintetizadas e secretadas pela glândula supra-renal que modulam uma vasta variedade de processos fisiológicos, incluindo a resposta ao stress, a resposta imuno-inflamatória, hidratos de carbono, o catabolismo de proteínas e carboidratos, níveis de electrólitos no sangue, e o comportamento. Os corticosteróides tópicos são os mais frequentemente usados em Medicina Dentária, focando-se principalmente na gestão sintomática das lesões da mucosa oral.

Objetivos: Este trabalho tem como objetivo rever na literatura atual o uso clínico de corticosteróides tópicos em prática de Medicina Dentária, ou seja, como abordagem terapêutica de algumas condições da mucosa oral, descrevendo as indicações, contra-indicações, vantagens e desvantagens da sua utilização, bem como as diferentes formas de administração (pomadas e géis adesivos, injeções intra-lesão, goteira individualizada) e regimes terapêuticos, para a optimização do tratamento.

Material e Métodos: Foi efetuada uma pesquisa nas bases de dados da Pubmed e Scopus, por artigos e referências relevantes. A seguinte combinação de palavras-chave foram usadas: “topical corticosteroids, corticosteroids, systemic corticosteroids, glucocorticoids, topical glucocorticoids, systemic glucocorticoids, treatment guidelines, pregnancy, oral pathology, dental medicine, oral mucosa, oral lichen planus, pemphigous, pemphigoid, recurrent aphthous stomatitis”. Maioritariamente artigos de revisão e investigação, ensaios e casos clínicos foram selecionados, com datas de publicação entre 2005 e 2016. Apenas artigos em português e inglês, com acesso ao texto completo e com relevância para o tema a descrever foram selecionados. Seguidamente, cada artigo foi avaliado pela análise do seu conteúdo.

Conclusão: Foram encontradas disponíveis guidelines relativas à aplicação tópica de corticosteróides, nomeadamente para o líquen plano oral e estomatite aftosa recorrente. No entanto, a abordagem terapêutica do pênfigo vulgar ou penfigóide bolhoso na Medicina Dentária não é clara, já que a maioria da literatura se refere a guidelines de dermatologia. Como a absorção pela pele não é como a da mucosa oral, mais estudos devem ser realizados no sentido de adequar as guidelines terapêuticas para as manifestações clínicas destas doenças na cavidade oral.

Introduction

Corticosteroids are steroid hormones synthesized and secreted by the adrenal gland that modulate a wide range of physiological processes, including stress response, immune-inflammatory response, carbohydrate and protein catabolism, blood electrolyte levels, and behaviour. ^(1, 2) Synthetic analogues can be produced and of clinical relevance for the modulations of distinct conditions. However, side effects are common and potentially problematic, such as the development of diabetes mellitus, hypertension, osteoporosis, weight gain, cataracts, Cushing syndrome, among others. ^(1, 3) These effects depend on the dose, duration of the treatment, rout of administration (for example: topic or systemic), among other factors. ^(1, 2)

In dental practice the use of corticosteroids for a long period of time is not very common, which carries lower risks for the development of chronic use-related complications. ⁽⁴⁾ Systemic corticosteroids are sometimes used following dental surgery (for instance for the management of the inflammatory response and edema formation associated with osteotomy). ⁽⁵⁾ Topic corticosteroids are more frequently used in the dental practice, generally focusing on the symptomatic management of oral mucosa conditions.

Oral local adverse reactions associated with topical corticosteroid therapy include secondary candidosis, mucosal atrophy, delayed cicatrization, refractory response, hypogeusia, burning mouth, hypersensitive reactions. ^(1, 2) Systemic adverse effects may include the inhibition of the hypothalamic-pituitary adrenal axis and secondary adrenal insufficiency, however these reactions only manifest in a small number of patients. ⁽²⁾

This work is set on the clinical use of topical corticosteroids in dental practice, namely for the management of oral mucosal conditions, embracing the indications, contraindications, advantages and disadvantages of their use, as well as the different forms of administration (use of adhesive ointments, gels, intra-lesion injections, costumized tray) and therapeutic regimens, for the optimizations of the clinical output.

Material and methods

The search for relevant references and articles was conducted in the PubMed and Scopus databases. The following combination of keywords was used: topical corticosteroids, corticosteroids, systemic corticosteroids, glucocorticoids, topical glucocorticoids, systemic glucocorticoids, treatment guidelines, pregnancy, oral pathology, dental medicine, oral mucosa, oral lichen planus, pemphigous, pemphigoid, recurrent aphthous stomatitis. Mainly review articles, research articles, clinical trials and case reports were selected, which publication date was comprehended between 2005 and 2016. Only papers in Portuguese or English, with access to the full text were chosen, according to their relevance to the theme to describe. Following, each article was evaluated for inclusion by its content analysis.

Glucocorticoids

Steroids were identified in the 1940's and since then, synthetic analogues have served a large range of uses, being applied for the management of inflammatory disorders, autoimmune diseases, antenatal use for preterm birth, and hematological cancers, among others. ⁽⁶⁻⁸⁾ Despite the huge advances in medicine since their discovery, a fully understanding of glucocorticoid action in physiological processes, such as inflammation, remains to be completely disclosed. ⁽⁹⁾

The term steroid can be applied to a plenteous variety of molecules which have different physiological effects. ⁽⁸⁾ Corticosteroids are a class of chemicals that include laboratory-synthesized and naturally produced hormones. ⁽⁸⁾ Corticosteroids include agents that have effects that can be uniquely glucocorticoid to uniquely mineralocorticoid. The first are responsible for the regulation of metabolism and inflammation, whereas mineralocorticoids regulate, essentially, sodium and water levels and excretion. The prescription of a steroid compound may have potent anti-inflammatory effects and additionally mineralocorticoid activity, which can cause significant adverse effects such as hyponatremia, hyperkalemia and hypotension, or the inverse, in mineralocorticoid excess states. ^(8, 10)

Glucocorticoids are catabolic steroid hormones synthesized and secreted by the adrenal gland as, among others, a response to stress. ^(7, 8, 10, 11)

The adrenal cortex is composed of 3 cellular zones, each one synthesizing a specific class of steroid hormones, i.e. mineralocorticoids, glucocorticoids and androgens, as seen in figure 1. ⁽⁴⁾

The principal mineralocorticoid is aldosterone (involved in the regulation of sodium and water levels) which is controlled by the angiotensin pathway; the principal glucocorticoid is cortisol, responsible for many physiological functions and metabolism regulation. ^(4, 10)

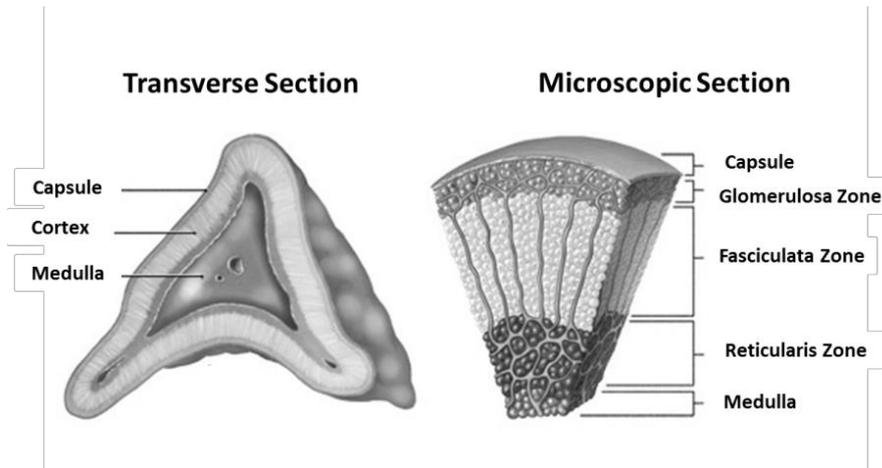


Figure 1: Transverse and microscopic sections of the adrenal cortex. Each one synthesizes a specific class of steroid hormones: glomerulosa zone secretes essentially, the mineralocorticoid aldosterone, fasciculada zone broadly synthesizes the glucocorticoid cortisol, and reticular zone broadly produces adrogens ⁽⁴⁵⁾

The release of steroids is regulated by an hormonal interplay system: stress conditions, hypoglicemia or trauma can stimulate hypothalamus to secret corticotrophin-releasing hormone (CRH), which acts on the anterior pituitary gland to induce the synthesis of adrenocorticotrophic hormone (ACTH), also known by corticotropin. In turn, this hormone acts on the adrenal cortex to stimulate the secretion of glucocorticoids (cortisol). ^(4, 7) This secretion is in a direct response to the action of ACTH. ⁽¹⁰⁾ Cortisol, as well as exogenous glucocorticoids, provide negative feedback on CRH release from the hypothalamus, and consequently on ACTH (fig.2). ⁽¹⁰⁾

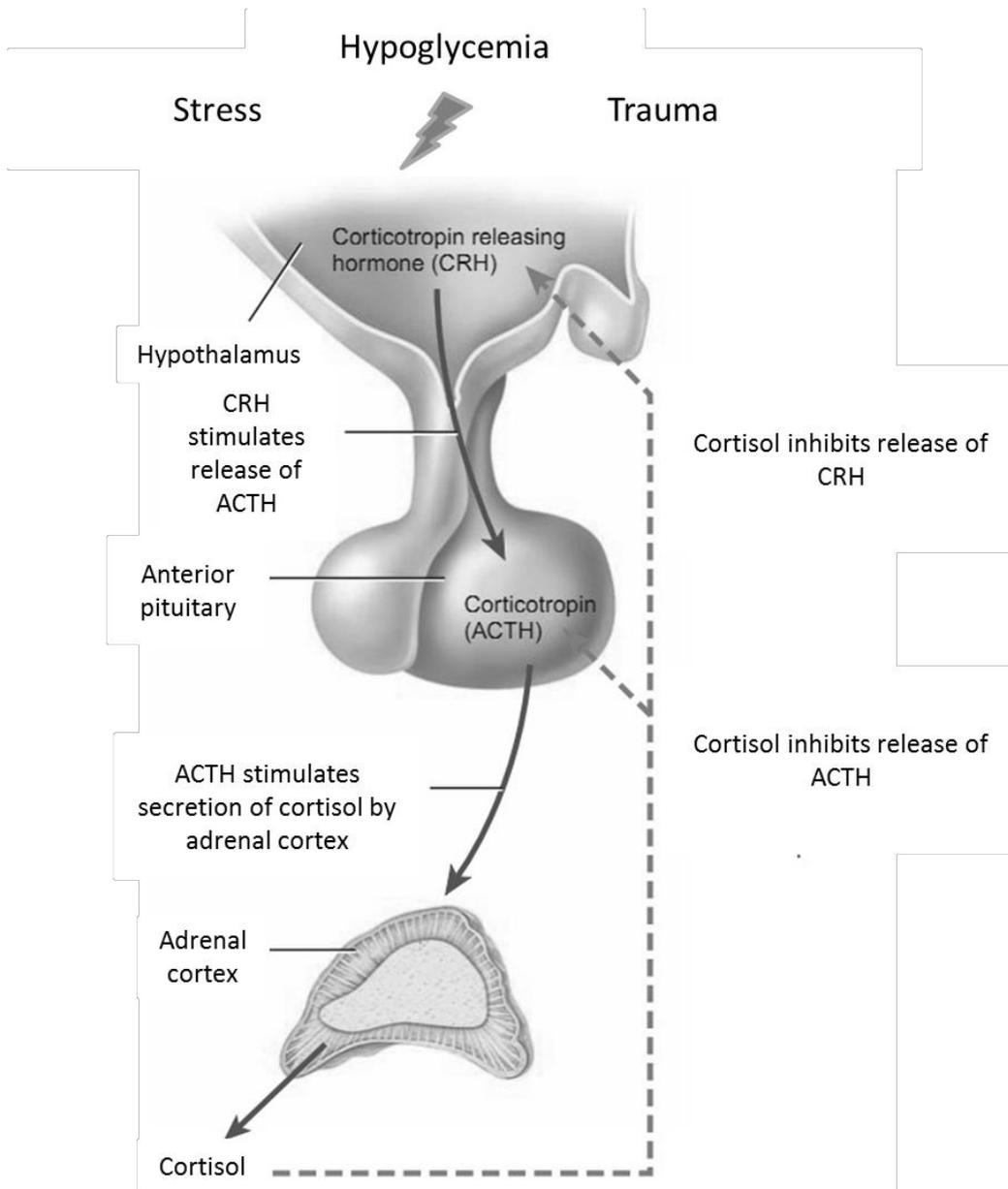


Figure 2: Mechanism of cortisol secretion and negative feedback regulation. (Adapted from Daniel E.Becker, 2013) ⁽⁴⁾

Glucocorticoids induce a variety of responses in virtually every tissue; in fact, they are important in metabolism, circadian rhythm, cell growth, reproduction and immunity. ^(12, 13) The mechanisms of glucocorticoids' actions are far more diverse and complex than previously thought, although most effects are known to be mediated by the glucocorticoid receptor. ^(12, 13) In the 1950's, it was found for the first time that cortisol can induce anti-inflammatory effects. Recent studies showed that physiological levels of glucocorticoids modulate inflammation and the immune functions, preventing excessive activation immune-inflammatory activation. ⁽⁴⁾

The inflammatory response

The inflammatory response is a physiological process that aims to restore tissue homeostasis. ⁽¹⁴⁾ The acute inflammation mechanisms are well understood. ⁽¹⁵⁾ Briefly, during an inflammatory response, exogenous or endogenous stimuli activate the tissue-resident macrophages, causing the release of inflammatory mediators, such as pro-inflammatory cytokines - tumour necrosis factor- α (TNF- α), prostaglandin E2, interleukin 1 (IL-1) and interleukin 6 (IL-6). ⁽¹⁵⁻¹⁷⁾ The inflammatory process characterizes itself by vascular dilation, increased blood flow, enhanced permeability of capillaries and leukocyte recruitment (in which polymorphonuclear neutrophils are the first recruited non-resident populations to the inflamed local; followed by mononuclear cells, monocytes and macrophages, that clear the cellular debris and phagocyte the apoptotic neutrophils). ⁽¹⁷⁾ The resolution of acute inflammation must be efficient, or neutrophil-mediated destruction, fibrosis or chronic inflammation may develop. ^(14, 17)

Glucocorticoids' anti-inflammatory activity

The anti-inflammatory activity of glucocorticoids is ascribed to the repression of pro-inflammatory genes (e.g., chemokines, adhesion molecules, receptors, cytokines, etc.) over signal transduction, by the glucocorticoid receptor (steroid receptor). ^(7, 12) Glucocorticoids are lipophilic, which gives them the ability to pass across cell membranes easily. Then, they bind to their specific intracellular receptor (glucocorticoid receptor), located in the cytoplasm, resulting in conformational changes, phosphorylation, dimerization and activation of the same. ^(11, 18) The binding is regulated by intracellular enzymes, being that the best described are the two types of 11 β -hydroxysteroid dehydrogenases (type 1 - 11 β -HSD1; type 2 - 11 β -HSD2), that can convert glucocorticoids in active or inactive forms. ⁽¹⁸⁾ Type 1 converts cortisone (inactive form) in cortisol (active form) and is expressed in the liver, muscle, pancreas, adipose tissue, bone and other tissues related to energy and metabolism; whereas type 2 inactivates cortisol and corticosterone (active forms) in cortisone and dehydrocorticosterone, respectively (inactive forms), and its expression is limited to cells involved in sodium homeostasis, like kidney, colon, sweat and salivary glands. ⁽¹⁸⁾ Next, the complex receptor-steroid migrates into the nucleus, binding to DNA, altering the genetic synthesis of proteins. ⁽⁴⁾ In consequence, cellular functions are modified: reduction of the production of enzymes responsible for regulating the synthesis of

inflammatory autacoids and immune-related cytokines, prostaglandins inhibition (which contributes to their analgesic effect), among others. ^(4, 5) All these effects converge to the suppression of vascular changes (which are accountable for the cardinal signs of inflammation). ⁽⁴⁾

The glucocorticoid receptor can regulate gene expression positively or negatively. They can bind to palindromic glucocorticoid response elements (GREs) in the promoters of target genes or interact with other transcription factors, such as nuclear factor κ B (NF- κ B), or activator protein-1 (AP-1). ⁽¹²⁾

MAPKs (Mitogen – activated protein kinases) are signalling proteins capable of using the extracellular stimuli as a mean of activation of the intracellular transduction pathways, via phosphorylation of a cascade of substrates. They regulate various physiologic cell processes, such as proliferation, apoptosis, development, differentiation, etc. If inappropriately activated by extracellular stimuli (for instance lipopolysaccharide, pro-inflammatory cytokines, cellular stress, among others), these induce the expression of inflammatory genes, perpetuating inflammation. In mammals, at least 4 subfamilies of MAPKs are known: extracellular signal-regulated kinases (ERKs), c-Jun NH₂-terminal kinases (JNKs), p38 isoforms (p38s) and (ERK5). ⁽¹²⁾

Glucocorticoids can exert their anti-inflammatory effects by interfering negatively with MAPKs signalling pathways. MAPKs activate inflammatory cells and mediators in lymphocytes, macrophages, neutrophils and mast cells; in these inflammatory cells, glucocorticoids inhibit the transcription factors that regulate the inflammatory cytokines and the production of inflammatory lipids. ⁽¹²⁾

The GR can also induce the expression of anti-inflammatory proteins, such as annexin-1 (Anx-1), MAPK phosphatase-1 (MPK-1) and glucocorticoid-induced leucine zipper (GILZ), by a transactivation mechanism and through post-genomic effects. ⁽¹²⁾ There is evidence that glucocorticoids can also have nongenomic actions capable of producing additional effects in various tissues. At a central level, excessive corticosteroids synthesis can lead to euphoria and psychosis, while deficiency can result in apathy, lethargy and depression. These effects may happen in the first minutes of exposure, however the process is not yet quite understood. ⁽⁴⁾

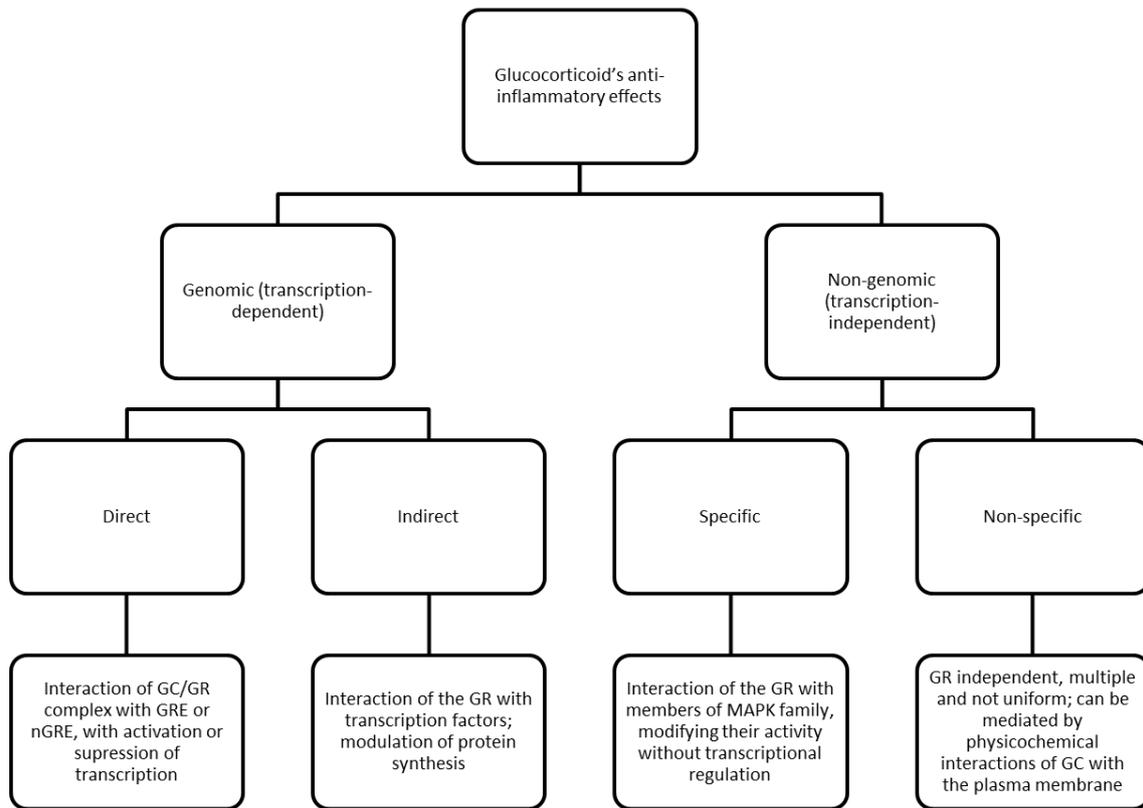


Figure 3:Schematic illustration of the glucocorticoids anti-inflammatory effects ^(7, 12)

So, in resume, glucocorticoids have the capacity of inhibit vascular dilation, liquid transudation, edema formation, decrease cell exudates, reduce fibrin deposit in the inflamed area, among others. The principal mechanisms responsible for these actions consist in the inhibition of leukocyte chemotaxis, inhibition of fibroblast function and endothelial cells, reduction of a variety of chemical inflammation mediators, and antiproliferative activity. ^(5, 19)

Indications

Glucocorticoids have many indications due to their various properties such as being anti-inflammatory, immunosuppressive, antiproliferative, analgesic and antiemetic agents. ^(11, 13, 19)

Table I: Resume of the glucocorticoid's indications based on their properties ^(11, 13, 19)

Properties	Applications
Anti-inflammatory	Imuno-inflammatory conditions such as asthma, rheumatoid arthritis, lupus erythematosus, lichen planus, pemphigus, pemphigoid, recurrent aphthous
Immunosuppressive/Imunomodulatory	Organ transplant recipients to prevent graft rejection, modulation of severe allergic reactions, autoimmune flare-ups
Antiproliferative	Hematologic malignances and as a complementary medication in certain chemotherapeutic treatments
Analgesic	Adjuvant analgesic for cancer pain
Antiemetics	Chemotherapy-induced and postoperative nausea

Side effects and contraindications

Although glucocorticoids have a wide application in distinct pathological conditions, relevant side effects are common and potentially problematic, especially with prolonged use. ^(4, 8, 20) Studies show that adverse effects occur in up to 90% of the patients who take glucocorticoids for more than 60 days, even if it is a low dosage, like less than 7.5mg/d, while short term use (described by some authors as 1 week) is relatively safe. ^(4, 8)

Some of the adverse effects are: the development of diabetes mellitus, hypertension, gastritis, gastrointestinal haemorrhage, peptic ulceration, osteoporosis, weight gain, dyslipidemia, cataracts, Cushing syndrome, adrenal suppression (Addison disease) skin changes, muscle weakness, among others, due to their effects on systemic energy balance. Further, psychiatric side effects, such as mood disorders, anxiety, delirium, panic disorder, have also been described. ^(8, 20-22)

Osteoporosis and osteopenia are due to the inhibition of calcium absorption in the gastrointestinal tract and increased bone resorption. For long term steroid therapy, when the potential risk of bone complication is expected, the prescription of calcium supplements with vitamin D to doses ≥ 5 mg / day, and bisphosphonates, if indicated by densitometry, could be considered. Bisphosphonates have the ability to prevent osteoclastic bone resorption, however, these are also associated with atypical fractures and osteonecrosis of the jaw; being the risk is higher after the administration of endovenous bisphosphonates. ^(8, 22, 23) However, calcium and vitamin D are not enough to prevent the bone loss attained with long term steroid therapy. ⁽²²⁾

Cushing's syndrome is a pathology caused due to chronic exposure to excess cortisol. It's clinical presentation is related to the extend and duration of the excess, however some signs and symptoms are unmistakable like muscle weakness, increased fat in the abdomen, torso and face and wide purple striae. ⁽²⁴⁾ Adrenal suppression usually goes "hand in hand" with the exogenous Cushing syndrome. Supraphysiologic or prolonged doses can lead to the suppression of the endogenous cortisol production, resulting in subsequent atrophy of the adrenal cortex. ⁽²¹⁾

Cushing's syndrome and adrenal suppression have been observed not only in patients taking oral glucocorticoids, but also with intra-articular, epidural, inhaled, ocular, and topic preparations. In Cushing's syndrome, it's possible to identify signs and symptoms of mineralocorticoid excess, since endogenous glucocorticoids also act on mineralocorticoid receptors. ⁽⁸⁾

Addison disease is a rare pathology also known as primary adrenal insufficiency, which in most cases is caused by auto-immune destruction of the adrenal cortex. ⁽²⁵⁾

Addison disease can be directly induced by exogenous glucocorticoids, through negative feedback of the HPA axis. ⁽⁸⁾

The risk for cardiovascular events (e.g. heart failure, ischemic heart disease) is increased in patients under GC therapy, due to potential development of hypertension, dyslipidemia, diabetes, among others. ^(22, 23)

Glucocorticoids have immunosuppressive effects that are capable of increasing host susceptibility to viral, bacterial, fungal, and parasitic infections; these, if present, constitute an absolute contraindication for the use of glucocorticoids. ^(23, 26)

There has been a concern regarding glucocorticoids association with immune-related cancers. Some studies show a possible association of squamous cell carcinoma and bladder cancer with GC use. ⁽²³⁾

Other alterations, such as avascular necrosis can be a side effect of glucocorticoids' therapy, particularly identified within the femoral head, by a mechanism not fully understood yet. ⁽²²⁾

Relative contraindications to the use of glucocorticoids include heart and kidney diseases, osteoporosis, diabetes, hypertension, peptic ulceration, among others, once these can potentiate the side effects of the medication itself, leading to life threatening events. ^(4, 22) Pregnancy and lactation are also relative contraindications for the glucocorticoid therapy. Some studies show that systemic glucocorticoids have a significantly increased risk of oral cleft development with first-trimester exposure. ⁽³⁾

To minimize systemic side effects, the use of alternative ways of administration, the use of the lowest dosage with therapeutic effects, and the use within the least amount of time, are recommended strategies. ^(19, 23) Careful monitoring and preventive strategies may also minimize side effects. ⁽²²⁾

Given the effects that glucocorticoids may have, especially in the HPA axis, one must be careful when stopping the administration. Low doses administered for a short period of time can be discontinued without tapering; higher doses and/or long term therapies may need tapering, which should be based upon clinical conditions (for example: established HPA axis dysfunction, patients under stress, etc.). ^(8, 27)

Interactions with other drugs

Patients with higher risk of drug interactions are infants, children and elderly, those with multiple diseases, those who are on multiple drug therapy and those with hepatic or renal disease.⁽²⁷⁾

The major interactions of glucocorticoids with other drugs are the ones that either inhibit (such as rifampicin) or induce (such as cyclosporine) their metabolism. It's particular important to be careful when prescribing drugs with a narrow therapeutic window, such as: warfarin, cyclosporine, doxepin, digoxin, theophylline and methotrexate, since in this cases, the amount of drug needed to produce the desired therapeutic effect is very close to the dose that can be toxic. For instance, the concomitant therapy of GCs with methotrexate is associated with increased hepatotoxicity.⁽²⁷⁾

Some studies show a negative correlation between steroid treatment and the concomitant use of antibacterial agents, as the presence of steroids causes a biofilm conversion, which correlates with increased colonization persistence and enhanced antibiotic tolerance.⁽²⁸⁾

The use of glucocorticoids and non-steroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen) seems to have a synergic effect regarding the increase on the risk of peptic ulceration and gastrointestinal bleeding. Therefore, caution should be exercised when using this combination.^(22, 29, 30) Some studies have also reported that the use of COX-2 inhibitors and glucocorticoids could increase the prevalence of gastrointestinal events.⁽²⁹⁾

Antifungals like ketoconazole and itraconazole increase the plasma levels of methylprednisolone and dexamethasone.⁽²⁷⁾

Macrolides are responsible for increasing therapeutic and adverse effects of methylprednisolone.⁽²⁷⁾

Glucocorticoids may antagonize the medication used in hypertension or diabetes, therefore destabilizing patients that were otherwise controlled.⁽²⁷⁾

As glucocorticoids have the capacity of suppressing the immune system, live vaccines should not be given at the same time.⁽²⁷⁾

Use in Dental Practice

Regarding dental practice, the use of corticosteroid therapy, for a long period of time, it is not very common, which carries a lower risk for the complications described with chronic use. ⁽⁴⁾

Systemic glucocorticoids are sometimes used in surgical procedures involving osteotomy, where we can expect an exaggerated inflammatory response, to better control inflammation and reduce edema formation. ^(2, 5) For instance, third molar extraction originates injury to the surrounding tissues, associated with pain, acute inflammation, and trismus, being corticosteroid therapy generally considered. ⁽⁵⁾ Additionally, these drugs are routinely used in severe lesions of the oral mucosa (which will permit a quicker resolution of the symptoms).

Prednisolone is the most common glucocorticoid prescribed for chronic conditions. It needs to be biotransformed to the active form, being it the reason why it is only available for oral use (allows first-pass metabolism during absorption). ⁽⁴⁾

Topic glucocorticoids

Topic glucocorticoids are one of the most prescribed drugs in oral pathology for treating atrophic erosive lesions that affect the oral mucosa. ⁽²⁾ Broadly, clobetasol propionate, fluocinonide and triamcinolone acetonide are the most commonly used GCs. ⁽²⁾ Attention should be given to the fact that the use of topical glucocorticoids is set on the symptomatic treatment, and not on the curative approach of oral conditions, being the discontinuing of the GCs use, often followed by recurrence of the symptoms of the disease. ⁽²⁾

Topic use is associated with a strong local anti-inflammatory and immunosuppressive activity, being well tolerated. ^(1, 2) Nevertheless, oral local adverse reactions include secondary candidosis, mucosal atrophy, delayed cicatrization, refractory response, hypogeusia, burning mouth, hypersensitive reactions. ^(1, 2) The refractory response can occur due to different reasons, such as poor patient compliance, bad instructions and patient use or inappropriate application. ⁽¹⁾

Furthermore, systemic absorption of topical applications continues to bring some concerns, as absorption through to oral mucosa is verified. However, clinical experience and most studies have shown no clinical significance of this situation in the majority of cases. ⁽¹⁾

Still, exceptions arise and systemic adverse effects, such as inhibition of the hypothalamic-pituitary adrenal axis and secondary adrenal insufficiency, nausea, among others, were verified in a small number of patients.^(1,2)

Following the rule, glucocorticoids should be avoided in growing children (because of their interference in the development), but if absolutely necessary, the intermittent use of medium potency glucocorticoids is often the choice, because it can thus reduce the development of adverse effects.⁽¹⁾

Topical glucocorticoids appear to be safe during pregnancy; however, their use should be further investigated due to the absence of data. Nevertheless, mild to moderate-potency topical glucocorticoids should be preferred, for the shortest time possible.⁽³¹⁾

The short time use (2-6 days) is indicated in diseases which have the natural tendency to spontaneous resolution, reducing its duration, and symptoms, as well.⁽²⁾ The prolonged use is eligible to chronic or very recurrent erosive lesions, like oral lichen planus (OLP), mucous membrane pemphigoid and some forms of complex recurrent aphthous stomatitis.⁽²⁾

When treating mucosal lesions, topical ointments or rinses are normally preferred.⁽⁴⁾

However the efficacy of the treatment depends on the time that the glucocorticoid is in contact with the lesion; in the oral mucosa due to saliva, movement of the tongue, among other reasons, it's difficult to keep the ointment for the necessary amount of time. For this reason, adhesive ointments are often used in customized trays, aiming the improvement of the treatment.⁽²⁾ To create an adhesive ointment, adhesive pastes for dentures can be used, given that studies support its good adherent qualities and clinical success. This technique should be used when treating small, isolated lesion or few lesions easily accessible. It's difficult to apply the medication in deep or large lesions and be certain that the drug is equally spread.⁽²⁾ If the lesions are situated on the gums or palate, the medication can be applied with the help of a customized tray (or in denture if the patient is edentulous), allowing perfect control of the amount of time that the drug is in contact with the lesions.⁽²⁾

Glucocorticoids can also be applied in aqueous solutions. This has great advantages like the capacity of controlling perfectly the time of exposition to the lesions, contact with all lesions regardless if they are large or deep and easier manipulation. However, it has also some disadvantages such as all mucosa (healthy or not) comes in contact with the medication, increasing systemic absorption and the risk of involuntary ingestion.⁽²⁾

Literature gives greater attention to clobetasol propionate, fluocinonide and triamcinolone acetonide, whose principal characteristics are described in the table below⁽²⁾:

Table II: Summary of principal characteristics of the most commonly used topical glucocorticoids prescribed in oral pathology ⁽²⁾

	Potency	Recommended Concentration	Applications
Clobetasol propionate	High	0,025% - 0,05%	2-3 x/day 3-5 min
Fluocinonide	Moderate-high	0,025% - 0,05%	5-10 x/day 3-5 min
Triamcinolone acetonide	Average	0,05% - 0,5%	3-10 x/day 3-5 min

Clobetasol propionate has the capacity to control rapidly the mucosal lesions, with a low number of applications each day, allowing longer lesion-free periods after the discontinuing of the treatment. Also, it can be used in severe erosive lesions with efficacy, allowing for an adequate control with topic administration.⁽²⁾

Fluocinonide is less effective in pain controlling than clobetasol.⁽²⁾

Triamcinolone acetonide is also very commonly prescribed within the management of oral mucosa lesions. However, some authors disclose its limitations, since it needs several applications during the day, which is a major inconvenience to the patient and can lead to failure of treatment efficacy.⁽²⁾

Oral Pathology

Oral Lichen Planus

Oral lichen planus (OLP) is a chronic inflammatory, mucocutaneous disease, associated with cell-mediated immunological dysfunction, that affects the oral mucosa, skin, genital mucosa, scalp and nails. ⁽³²⁻³⁴⁾ Its etiology is yet unknown. ⁽³³⁾ This disease is most seen in middle-aged patients, primarily in women. ⁽³²⁾ Commonly, it affects the oral mucosa without the presence of skin lesions. ⁽³⁴⁾

OLP is described in six types of clinical variants: reticular, popular, plaque-like, erosive, atrophic and bullous. It is possible to have multiple or coexistent forms, in the same patient. Clinically it may exhibit in various manifestations such as white striations (known as Wickham's striae, which are a characteristic feature), white papules, white plaque (this form may be difficult to differentiate from leucoplakia), erythema, erosion or blisters (however this is rare). ^(33, 34) OLP generally occurs in the buccal mucosa, tongue, gingiva, mucobuccal area, while mucosa of palate and floor of the mouth are rarely affected ^(32, 35) Its most common form is the reticular lesion, followed by erosive, atrophic and plaque types. ^(32, 35) Reticular form expresses the typical Wickham's striae and is often asymptomatic; wheatear it should be controlled (1 year follow up), since it can evolve to a symptomatic form: ulcerative (erosive) or atrophic. ⁽³²⁻³⁴⁾ These forms can cause burning sensations and severe pain, associated with a risk of malignant transformation, particularly lesions of the tongue. ⁽³²⁾

The classic histologic characteristics are band-like dense inflammatory infiltrate of T lymphocytes, hyperparakeratosis with thickening of the granular cell layer, liquefactive degeneration of basal keratinocytes, Civatte bodies, saw-tooth appearance of rete ridges and normal maturation epithelium. ⁽³³⁻³⁷⁾



Figure 4: Presence of oral lichen planus on the oral mucosa (right cheek). Courtesy of Prof. Dr. Otilia Lopes



Figure 5: Presence of erosive oral lichen planus on the oral mucosa (left cheek). Courtesy of Prof. Dr. Otilia Lopes

Treatment

Various treatments have been used to manage the symptomatic oral lichen planus, with variable results, such as: topical retinoids, topical calcineurin inhibitors (like tacrolimus, pimecrolimus), photochemotherapy, photodynamic therapy, among others. ^(33, 35)

Glucocorticoids are the most used due to their activity in suppressing cell mediated immune activity, more specifically, topical glucocorticoids are the first-line therapy for mucosal erosive

lichen planus; they are able to improve some of the components of the lesion, however the underlying and persistent immune mechanisms remain active. ^(2, 36) Specific protocols can be used for individual patients based on their lesion characteristics. ⁽²⁾

Systemic glucocorticoids, like prednisolone, are used only in severe, resistant, widespread oral lichen planus. ^(34, 36)

Table III: Evidence basis for the value of topical glucocorticoids in the treatment of Oral Lichen Planus (Adapted from Al-Hashimi et al, 2007) ^(34, 38, 39)

Topical glucocorticoid	Form of administration	Indication
Clobetasol propionate 0.025%	Ointment – applied 2X/day for the first month, then 1X/day for the second month	Treatment of choice for symptomatic atrophic/erosive OLP
Clobetasol propionate 0.05%	Ointment – gingival trays for at least ½ hour a day, 2X/day for 6 weeks	Mixed atrophic-erosive, hyperkeratotic OLP with strong gingival involvement
Clobetasol propionate 0.05%	Mouthwash – 2 to 3X/day	Severe erosive oral lichen planus lesions
Triamcinolone acetonide 0.1%	Mixed with orabase – applied 3 times daily, until symptoms improve	Treatment of choice for symptomatic atrophic/erosive OLP
Triamcinolone acetonide 0.1%	Mouthwash – rinse for 4 weeks	Generalized lesions of symptomatic OLP
Fluocinolone acetonide 0.1%	Orabase – applied 4X/day for 1 month	Chronic symptomatic atrophic/erosive OLP

Studies show that when using triamcinolone acetonide at 0.0025%, 25% of the patients with oral lichen planus achieve complete resolution of the lesions.⁽²⁾ Other study reported that the use of fluocinolone acetonide should be preferred because will be no permanent adrenal cortical suppression and it's more effective than triamcinolone acetonide.⁽³³⁾

Other topical glucocorticoids that can be used are: fluticasone propionate, betamethasone sodium phosphate and mometasone. These are less explored; however some studies reported very good results with mometasone with minimal side effects.⁽²⁾

Oral lichen planus may have an unpredictable response to the glucocorticoids, so it's possible that some times, the white lesions can become even whiter. There are some areas that respond worse to the treatment, like the mucosal atrophy; even after the treatment these areas can still have atrophy characteristics.⁽²⁾

It's very common to have a secondary candidiasis during the treatment (it's the most frequent of the side effects), so prescribing Nystatin either in cream or aqueous form is an option to reduce it.^(1, 2, 34)

Despite the verified evidence, there is a need for more studies to standardize the methodology for the treatment of OLP with both topical and systemic glucocorticoids.

Pemphigus

Pemphigus is a rare, serious autoimmune disease that causes blistering of the skin and oral cavity. If left untreated, it is often fatal.^(40, 41) Two basic forms of this condition are acknowledged: pemphigus vulgaris and pemphigus foliaceus, although oral lesions do not occur in pemphigus foliaceus. Pemphigus vulgaris affects the basal-cell layer and is associated with auto-antibodies to desmoglein 3 (which is a keratinocyte cell-surface adhesion molecule) and it's most commonly diagnosed in the fourth to sixth decades.⁽⁴¹⁾

Pemphigus vulgaris is characterized clinically by oral pain, presence of erosions and superficial ulcerations at different sites of the oral mucosa, preferably in oral and labial mucosa, ventral surface of the tongue, palate and gums (can also be recognized as *gingivitis descamativa*). Rarely vesicles or intraoral bubbles are identified, possibly by the friability of the lesions. A bubble can be produced in the mucosa or normal-looking skin if pressure is imposed on its surface. This is called Nikolsky positive sign.^(40, 41)

To diagnose pemphigus vulgaris, we can resort to its clinic, histopathological and immunological characteristics.⁽⁴⁰⁾

Its etiopathogenesis is related to an immune response, wherein auto-antibodies are directed into keratinocytes antigens, which results in the separation of these cells from one another (a process known as acantholysis), which in turn originates bulla, as described in figure 3. ^(40, 41)

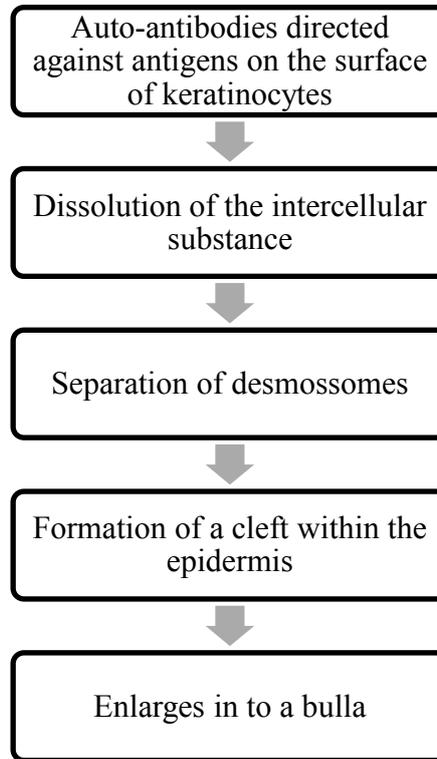


Figure 6: Diagram representing the process of acantholysis resulting from the attack of the auto-antibodies to the antigens of keratinocytes.⁽⁴¹⁾

The most relevant histological characteristics of oral pemphigus vulgaris are: presence of intraepithelial cleft located above the basal-cell layer, acantholysis, Tzanck cells (round cells with acantholysis present in area) and a mild to moderate chronic inflammatory infiltrate in the underlying connective tissue. ^(40, 41)

Treatment

The treatment can be divided in three phases: control, consolidation, maintenance. ⁽⁴¹⁾ The control phase is the period in which the intensity of therapy is higher. The aim is to inhibit the formation of new lesions and start the healing process. If the right dose of medication is given, an adequate treatment response can be verified in 2 weeks. The consolidation phase is the period in which the intensity of the therapy needed to control the disease is maintained until 80% of previous lesions have healed. At last, the maintenance phase is the period in which the intensity of the therapy is gradually reduced. ⁽⁴¹⁾

Oral lesions can be treated with potent topical glucocorticoids, such as clobetasol propionate 0.05%, mixed with adhesive paste, fluocinonide 0.05% and dexamethasone elixir, 2 to 3 applications a day for 3 to 5 minutes as described in literature. ⁽²⁾ For gums and hard palate, customized acrylic trays can be used. Similar results are achieved with intralesional injections of triamcinolone acetonide diluted to 10mg/mL. ^(41, 42)

Systemic therapy for pemphigus may be administered orally. The most used glucocorticoid is prednisolone, and the administration protocol depends on the severity of the disease. The initial recommended dose of prednisone is 0.5–2 mg/kg. Depending on the response, the dose can be decreased slowly to the minimum therapeutic dose, taken once a day in the morning to minimize side effects. ⁽⁴⁰⁾ If with the topical treatment, new lesions still form, it can be administered a low dose of prednisolone: 20 to 40mg /day; if the patient doesn't respond to the treatment, we can increase the dose to 70 to 90 mg/day, which is a moderately high dose. ⁽⁴¹⁾

There is not much information about doses and posology to use in dentistry, especially for the topical treatment so more studies are needed.

Bullous pemphigoid

Bullous pemphigoid is a chronic autoimmune disease that affects most the elderly after the seventh decade. ⁽⁴³⁾ It is characterized by an autoimmunity activation (as pemphigus and other autoimmune diseases) due to the loss of self-tolerance in T and B lymphocytes, more specifically, an auto-antibody response against structural components of hemidesmosomes, resulting in sub-epidermal blistering. ^(43, 44) Bullous pemphigoid may have spontaneous exacerbation and remission phases. ⁽⁴³⁾ Generally, it is characterized by a nonbullous phase, in which the manifestations are nonspecific: pruritus, excoriated, eczematous, papular, and or fixed

urticarial-like lesions. These can persist for several months or be the only sign of this pathology. The bullous phase is characterized by large and tense blisters with round or oval shape. Oral mucosa is involved in 10% to 25% of the patients.⁽⁴⁴⁾

The bullous pemphigoid etiopathogenesis is not fully understood yet, but it is thought that some factors may contribute, such as drug intake, physical agents, viral infections and diet.⁽⁴⁴⁾

The mechanism responsible for the blisters formation is resumed in the diagram below (see figure 4).⁽⁴⁴⁾

The principal histological characteristics are sub-epidermal blister with superficial dermal inflammation (presence of lymphocytes, histiocytes and eosinophils).⁽⁴⁴⁾

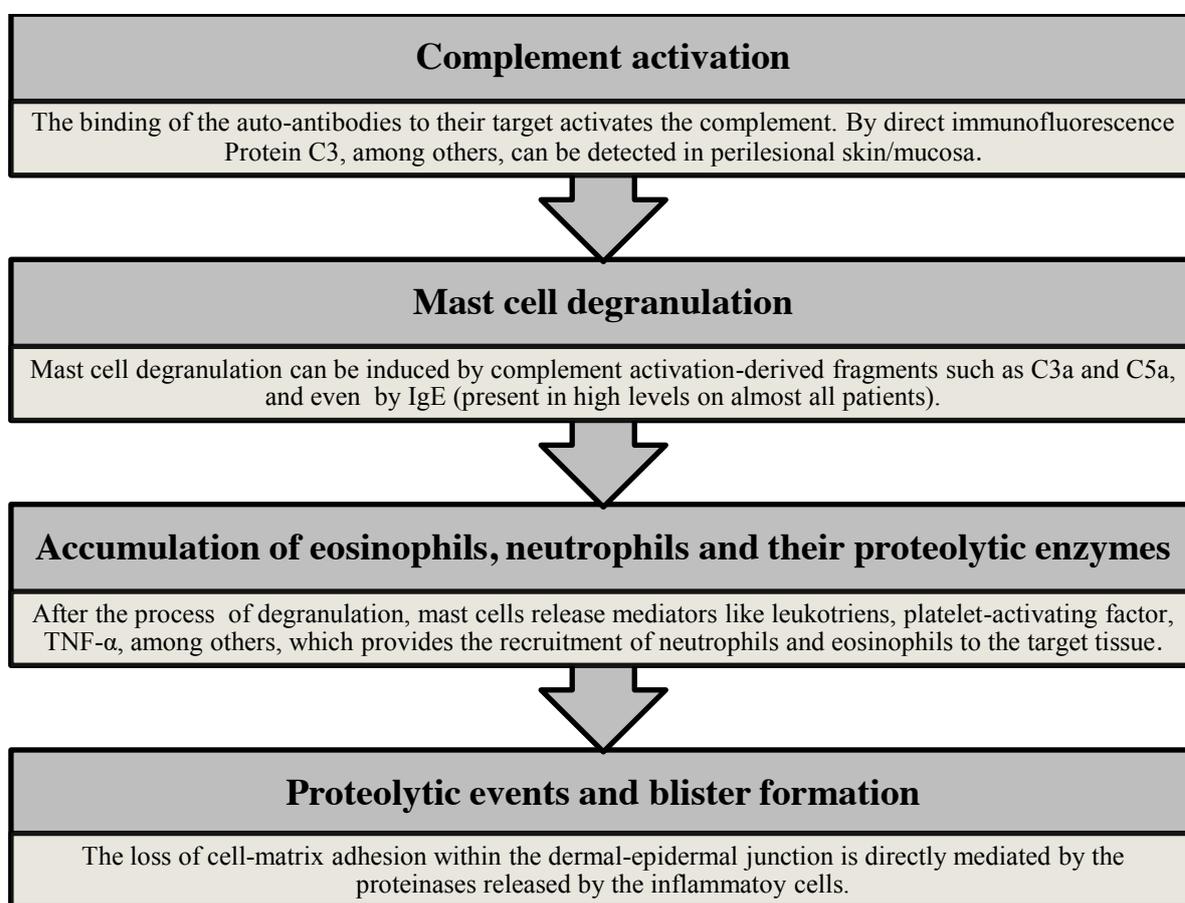


Figure 7: Diagram explaining the process of auto-immune activation that leads to the blister formation in Bullous pemphigoid.⁽⁴⁴⁾



Figure 8: Presence of bullous pemphigoid lesions on the oral mucosa. Courtesy of Prof. Dr. Otilia Lopes

Treatment

The management of bullous pemphigoid depends on its multifactorial pathogenesis; however, systemic glucocorticoids are still the first choice for the treatment of this disease. A dose of prednisolone 0.75mg to 1.00mg/Kg/day or less should be the necessary to maintain the disease controlled. Once the blisters stop, its development and erythema has reduced, tapering of prednisolone is recommended. This is usually achieved by the end of second week of therapy. The use of topical therapy alone is a valid alternative to the systemic use. ⁽⁴³⁾ There are no guidelines available for the dental management of this condition, only for dermatologic management, and as absorption by the skin is not the same as the one as in the oral mucosa (since the latter is more irrigated and thinner, grating the absorption faster and more complete) and also by the fact that the lesions do not have the same characteristics. In this way, the corticosteroid dosage may be different, so more studies are required.

Recurrent aphthous stomatitis

The recurrent aphthous stomatitis is a chronic inflammatory pathology very common in the oral mucosa. ^(45, 46) Its most characteristic symptom is the recurrent onset of single or multiple erosions and ulcers; these appear mainly on unattached oral mucosa of the lips, cheeks and tongue, however it is possible to be observed on keratinized palatal and gingiva mucosa. ⁽⁴⁵⁾

The recurrent aphthous stomatitis may be divided in three forms: recurrent aphthous stomatitis minor, major and the herpetiform. ⁽⁴⁵⁾ The minor form is the most usual. The second one it's frequently found in patients infected with HIV. ⁽⁴⁶⁾ In the last one, ulcers may coalesce to form larger ulcers with marked erythema. ⁽⁴⁶⁾ The principal characteristics of these conditions are described in the table below:

Table IV: Principal clinical characteristics of the 3 forms of recurrent aphthous stomatitis (RAS) (Adapted from Zuzzana S. et al, 2014) ^(45, 46)

Type of RAS	Size (mm)	Number of lesions	Depth	Scar	Duration (days)	Peek onset (age)	Localization
Minor	5-10	<10	Shallow	No	10-14	2nd decade life	Non keratinized oral mucosa; more common: lips, buccal regions, tongue margins
Major	>10	1-3	Deep	Yes	>14	1st and 2nd decades of life	Keratinized and non-keratinized oral mucosa; more common: soft palate, lips, tongue, palatal fauces
Herpetiform	<5	>10	Shallow	No	10-14	3rd decades of life	Non keratinized oral mucosa; more common: floor of the mouth, ventral surface of the tongue

Its pathogenesis is still not known, however both local and systemic factors can be associated with it; it's also thought that an immune-mediated reaction (lesions arise as a consequence of immunologically mediated cytotoxicity of epithelial cells) exists. ^(45, 46)

Diagnose is made after clinical exam, with detailed history and examination of the ulcers. ⁽⁴⁶⁾

Histological characteristics include massive leukocytic infiltration (that can be different according with the severity and duration of the disease); before the ulcer formation, monocytes

and lymphocytes (principally T type) infiltration, with single mast and plasmatic cells under the basal cell layer. After the ulcer formation, polynuclear leukocytes recruitment occurs to the center of the ulcer, with mononuclear cell infiltration on the lesion border. ⁽⁴⁶⁾



Figure 9: Presence of major ulcer on the lips. Courtesy of Prof. Dr. Otilia Lopes

Treatment

The principal aim of the treatment is to decrease the symptoms, reduce ulcer number and increase the disease-free period. ⁽⁴⁷⁾

Topical medication is often the first choice, such as triamcinolone acetonide (orabase), intralesional injections), clobetasol propionate (orabase), fluocinonide ointment (orabase), (see table IV) and can often include the use of a chlorhexidine mouthwash (without alcohol base) or dexamethasone 0.05 mg / 5 ml (rinse and spit three times per day). The elixirs are most used when multiple ulcers are localized in soft palate or oropharynxes, as well as for multiple and diffuse ulcers. ⁽⁴⁷⁻⁴⁹⁾ See table IV.

Systemic treatment is recommended for severe, refractory, constantly recurring ulcerations. ⁽⁴⁶⁾ A short course of systemic glucocorticoid therapy (oral prednisolone) may be necessary, but it

shouldn't exceed more than 50 mg/day (preferably in the morning) for 5 days. Some studies refer we should start with 25mg/day. Tapering may be necessary. ^(48, 49)

Table V: Indications of topical glucocorticoids in the treatment of Recurrent Aphthous Stomatitis ^(48, 49)

Topical glucocorticoid	Form of administration	Indication
Triamcinolone acetonide 0.05-0.5%	Pomade orabase – 3 to 10X/day for 3 to 5 minutes	Localized ulcers, small and mild erosive lesions
Fluocinolone acetonide 0.025-0.05%	Pomade orabase – 5 to 10X/day for 3 to 5 minutes	Localized ulcers, however more aggressive
Clobetasol propionate 0.025%	Pomade orabase - 2 to 3X/day for 3 to 5 minutes	Localized ulcers with moderate or severe presentations
Triamcinolone acetonide Fluocinolone acetonide Clobetasol propionate	Rinses/Mouthwashes forms – 3 to 4X/ day 20-30 minutes without eating or drinking	Multiple, diffuse oral ulcers

Conclusion

Since its discovery, glucocorticoids have been widely used for the management of distinct conditions, being applied for the management of inflammatory disorders, autoimmune diseases, antenatal use for preterm birth, and hematological cancers, among others. However, when associated with treatments for long periods of time (particularly when using systemic glucocorticoids) a high incidence of adverse effects is verified. In dentistry, corticosteroids are commonly used for shorter periods of time and thus, fewer risks are broadly associated.

In the practice of dentistry, they are widely used in inflammatory diseases with an autoimmune nature, and to control inflammation. Systemic corticosteroids are frequently used to control inflammation in more invasive surgical procedures, as those including osteotomy. They can also be used as adjuvants in topical medication to control more severe lesions of the oral mucosa, wither erosive or refractory in nature.

On the other hand, topical corticosteroid therapy is commonly used for the management and control of immune-inflammatory conditions of the oral mucosa, being acetonide triamcinolone, fluocinolone acetonide and clobetasol propionate, the most commonly drugs. These can be used in different application forms: customized trays, adhesive (orabase) ointments, gels, intralesional injections and elixirs, being selected in accordance with the lesions characteristics.

Guidelines for treatment / maintenance of distinct conditions with topical corticosteroid therapy were found available, especially regarding oral lichen plan and recurrent aphthous stomatitis conditions. However, less is known regarding therapeutic management of pemphigus vulgaris or bullous pemphigoid, since the majority of the literature refers to dermatology guidelines. As absorption by the skin is not as the one in oral mucosa, more studies should be conducted in these areas in order to disclose therapeutic guidelines adequately focused on the oral management of these conditions.

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APPENDICES