Universidade de Lisboa

Faculdade de Farmácia

Corticosteroids and Oral Pathology of Autoimmune Mucocutaneous Diseases

Eduarda Maria Portela Teixeira da silva

Monografia orientada pela Professora Doutora Ana Francisca de Campos Simão Bettencourt, Professora Auxiliar com Agregação e coorientada pelo Professora Doutora Maria Cristina Bettencourt Neves, Professora Auxiliar com Agregação

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Monografia orientada pela Professora Doutora Ana Francisca de Campos Simão Bettencourt , Professora Auxiliar com Agregação da Faculdade de Farmácia da Universidade de Lisboa e coorientada pela Professora Doutora Maria Cristina Bettencourt Neves, Professora Auxiliar com Agregação da Faculdade de Medicina Dentária da Universidade de Lisboa

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Resumo

A cavidade oral, mais especificamente a mucosa oral, pode ser afetada por vírus, bactérias, fungos ou até mesmo por doenças de causa autoimune. Em particular, as doenças mucocutâneas de causa autoimune com expressão oral mais prevalente mundialmente são o Líquen Plano Oral, causados por lesões inflamatórias de natureza autoimune, o Pênfigo Vulgar e o Penfigoide Mucomembranoso, causado por lesões bolhosas intra e sub epiteliais respetivamente. É importante realçar que as três patologias mencionadas apresentam semelhanças entre si, no que concerne ao nível das manifestações clínicas ou na forma/meios de diagnóstico.

Os corticosteroides com o seu potencial anti-inflamatório, anti proliferativo e atividade vasoconstritora, descobertos há cerca de 60 anos, podem variar na sua eficácia terapêutica. Em relação a efeitos adversos, os corticosteroides causam sobretudo efeitos locais, mas se administrados em doses elevadas ou utilizados por longos períodos podem causar efeitos adversos sistémicos. Além de todos os problemas que os corticosteroides acarretam, também é necessário ter especial atenção à taquifilaxia (diminuição rápida do efeito do fármaco após repetição das doses).

De acordo com o algoritmo terapêutico de cada patologia, os corticosteroides consistem na primeira linha de tratamento, sendo que ao nível do Líquen Plano Oral, as formulações tópicas são as mais utilizadas, enquanto nas restantes duas patologias são mais utilizadas as formulações sistémicas, com a possibilidade de coajudvância com formulação tópica. Seguidamente, considerando vários fatores como a resolução ou não do problema e a duração do tratamento podem ser considerados ou novas formas farmacêuticas como as injeções intralesionais de corticosteroides ou novos grupos de fármacos como imunossupressores, anticorpos monoclonais ou até mesmo outras terapêuticas não convencionais como Terapia Psolareno + UVA (PUVA) ou laser de iodo.

As formas farmacêuticas dos corticosteroides disponíveis ao nível do mercado não são as mais adequadas para a utilização ao nível da mucosa oral, devido a vários fatores internos e externos. Como tal, surge a necessidade de comercializar novas farmacêuticas que sejam mais adequadas não só para as características da cavidade oral, mas também para as necessidades dos doentes, como a adesão à terapêutica. Assim sendo, surgem novas perspetivas no que diz respeito a formas farmacêuticas como hidrogeles, comprimidos bucais adesivos, micropartículas, lipossomas entre outras.

Palavras-chave: Líquen Plano Oral, Pênfigo Vulgar, Penfigoide Mucomembranoso, Corticosteroides, Tópicos

Abstract

The oral cavity, more specifically the oral mucous membranes, can be affected by viruses, bacteria, fungi, and autoimmune causes. Particularly, the oral mucocutaneous diseases of an autoimmune cause that have a higher prevalence worldwide are the Oral Lichen Planus, which may be caused by autoimmune inflammatory conditions, Pemphigus Vulgaris, and the Mucous Membrane Pemphigoid, which can be caused by intra-epithelial or sub-epithelial blistering respectively. The three mentioned pathologies have similitudes like the signals and symptoms and/or the forms and means of diagnosis.

Corticosteroids with their anti-inflammatory, anti-proliferative, and vasoconstrictor activity potential, discovered nearly 60 years ago, may vary their therapeutic efficacy. Regarding the adverse effects, the corticosteroids mainly cause local effects, but if administered in high dosages or used for long periods may cause systemic effects. Also, it is necessary to have special attention to tachyphylaxis (rapid decreases of the pharmacy effect after repetitive doses).

According to the therapeutic algorithm of each pathology, the corticosteroids consist in the first line of treatment, topical formulation for OLP, while in the other two pathologies it is preferable to use the systemic formulations with a possibility of reinforcement by topical corticosteroids. Therefore, considering various factors like the resolution of the problem and the duration of the treatment, it may be considered new pharmaceutical forms like the intra lesions injections or new therapeutic classes like immunosuppressor medicines, monoclonal antibodies, and even other non-conventional therapies like PUVA and iodine laser.

However, the corticosteroids available on the Portugal market in the existing pharmaceutical forms are not the most adequate to be administered buccally, due to internal and external factors. Consequently, there is a need to commercialize new pharmaceutical forms that are more suitable not only for the oral cavity characteristics but also for the needs of the patients, like compliance. Therefore, the new pharmaceutical forms appear as futures perspectives for this type of diseases like hydrogels, buccal adhesive tablets, microparticles, liposomes among others.

Keywords: Oral Lichen Planus, Pemphigus Vulgaris, Mucous Membrane Pemphigoid, Corticosteroids, Topical

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Abbreviations

- OLP – Oral Lichen Planus
- PV – Pemphigus Vulgaris
- MMP – Mucous Membrane Pemphigoid
- WHO – World Health Organization
- BMZ - Basement Membrane Zone
- AIBDs – Autoimmune Bullous Diseases
- LP – Lichen Planus
- SCC – Squamous Cell Carcinoma
- INF- Gamma – Interferon-Gamma
- TNF-α -Tumor Necrosis Factor Alpha
- CMV – Cytomegalovirus
- HSV-1 – Herpes Simplex Virus 1
- HHV – Human Herpesvirus 6
- EBV – Epstein-Barr Virus
- HBV – Hepatite B Virus
- HPV – Human Papilloma Virus
- HLA – Human Leukocyte Antigen System
- IgG – Immunoglobulin G
- Dsg-1 – Desmoglein 1
- Dsg-3 – Desmoglein 3
- C3 – Complement C3
- IgM – Immunoglobulin M
- IgA – Immunoglobulin A
- UV – Ultraviolet
- Anti-Dsg-1 -Antibody Desmoglein 1
- Anti-Dsg-3 – Antibody Desmoglein 3
- DIF – Direct Immunofluorescence
- IIF – Indirect Immunofluorescence
- ELISA – Enzyme-Linked Immunosorbent Assay
- IBD – Inflammatory Bowel Disease
- BNF – British National Formulary

- Hsp – Heat-shock proteins
- GRE – Glucocorticoid- Response Element
- AP1 – Activator Protein 1
- NKFB – Nuclear Factor KB
- IRF-3 – Interferon Regulatory Factor 3
- AVN – Avascular Bone Necrosis
- GT – Growth Hormone
- FTU – Fingertip Unit
- PUV A – Psoralen + Ultraviolet Radiation
- IV – Intravenous
- PDAI – Pemphigus Disease Area Index

General Index

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1. Introduction

The oral cavity consists of a presage indicator of diffuse lesions. Therefore, there is a chance to intercede early, which could result in a probable decrease in morbidity and mortality (1).

The mouth is constituted by various structures covered with mucosa membranes namely the tongue, gums, palate, cheeks, and lips. There are several pathologies from multiple etiologic factors, particularly viruses, bacteria, fungi, and not least important autoimmune. Therefore, the mucocutaneous diseases of autoimmune cause with a higher prevalence are the Oral Lichen Planus (OLP), Pemphigus Vulgaris (PV), and Mucous Membrane Pemphigoid (MMP) (2-4).

These diseases have differences from each other, specifically in the etiological factor and the form of treatment. Moreover, also share some similarities particularly theclinical manifestations and the way or means of diagnosis (5-20).

Therefore, the golden standard for treating these three pathologies consists of corticosteroids, which may differ if it is administered buccally for topical application or orally for systemic application (21-26).

Corticosteroids firstly synthesized between 1948 and 1952, have an anti-inflammatory, anti-proliferative, and vasoconstrictor activity, with a possibility of leading to local or systemic adverse effects, if used in a prolonged form or administered at high dosages (27-30).

Currently, there are plenty of pharmaceutical forms of different active principles of corticosteroids. However, these pharmaceutical forms are not the most adequate to be used in the oral mucosa due to several factors like the presence of saliva, saliva turnover, mechanical stress by surrounding muscles, and the presence of certain excipients like isopropyl alcohol, flavoring, and acid buffers, which could aggravate these diseases (31).

Therefore, there is a need to investigate and commercialize other pharmaceutical forms that are most suitable for the oral cavity, not only to bypass all the obstacles that

the oral cavity involves, but also with a superior benefit not only to the quality, efficacy, and safety of the medicine as well as the patients' compliance.

For that reason, this present monograph aims to review the mucocutaneous diseases associated with an autoimmune cause, namely the OLP, PV, and MMP, where are addressed the epidemiological characteristics, clinical manifestations, and forms of diagnosis, with a higher emphasis on the first-line treatment, but also discuss other pharmaceutical forms that show potential to be used in the oral cavity.

2. Materials and Methods

The elaboration of the present monography, "Corticosteroids and Mucocutaneous Diseases of an Autoimmune Cause "was obtained by conducting a literature review including the interpreting, and synthesis of a variety of scientific articles, obtained from different sources.

Bibliography sources were PubMed (https://pubmed.ncbi.nlm.nih.gov), and the World Health Organization (WHO) (https://www.who.int), as well as the search engines of Google and Google Scholar. Also, it was used the platforms Micromedex, UpToDate, and Infomed of Infarmed.

For the research different keywords were used: "Mucocutaneous Diseases", "Mucocutaneous Diseases of Autoimmune Cause", "Oral Lichen Planus", "Mucous Membrane Pemphigoid", "Pemphigus Vulgaris", "Corticosteroids", "Topical Corticosteroids", and "Systemic Corticosteroids".

The research was mostly made between the months of December and May of the present year of 2022. Moreover, it is important to refer that there wasn't a restricting in the publishing data, but there was a preference for the more recent publications, mostly the last 10 years. The articles that were used were in English, Portuguese, and Spanish language.

The scientific articles were selected based on abstract reading, their complete consultation reading, and references of articles read were also consulted.

Therefore, to carry out and elaborate on the bibliographic references, it was used a computer program named Mendeley. Also, they were elaborate according to the Vancouver style.

The present monograph follows the provisions of the MICF 2022 internal rules for the preparation and presentation of Monographs – Curricular Internship Regulation for the Integrated Master Course in Pharmaceutical Science (Diário da República, 2nd series, of December 18, regulation nr. 856/2006, regulated by Directive 2013/55/EU).

3. Mucocutaneous Diseases of Autoimmune Cause

According to the World Health Organization (WHO), health is defined as "complete physical, mental and social well-being, not just the absence of diseases or illness" (32). As stated in the Priberam Dictionary, the disease is marked as a lack of health (33).

Oral cavity diseases can be associated with more extensive injuries (1). Therefore, there is a chance to intercede prematurely, communicate with other health care professionals, and decrease morbidity (1). Normally, the point of origin of these diseases is the oral cavity, but they can spread to the skin or other mucous membranes (34).

The oral mucosa contains a stratified epithelial layer to protect against any chemical or physical harm (2,4). This layer's integrity depends on structures that sustain the cell-cell adhesion like desmosomes and adherents' junctions and the cell-matrix adherence such as the hemidesmosomes and focal contacts as shown in Figure 1 (3,4). The Basal Membrane Zone (BMZ) is composed of the basal cell plasma membrane, the lamina lucida, the lamina densa, and the sublamina densa, which comprises a mix of structural constituents and antigens like collagen VII and collagen IV (4).

The oral cavity can be affected by diseases of autoimmune cause also designated Autoimmune Bullous Diseases (AIBDs), which are a group of chronic inflammatory illnesses where autoantibodies are against structural proteins that exist in the skin or the mucosa that can cause blistering. There are various diseases, but the most prevalent AIBDs, that are the matter of discussion in this thesis are the OLP, PV, and MMP (3,4).

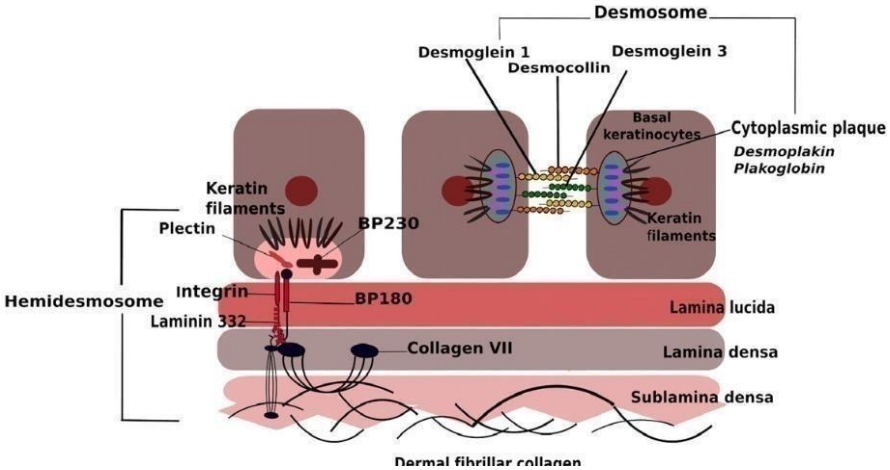


Figure 1 - Schematic Representative of the Oral Mucosa (4)

3.1. Oral Lichen Planus

Lichen Plan (LP) is named after a Greek word, leichen, with a significance of tree moss, and planus derives from Latin, with a definition of flat. Firstly, reported in 1869 by the British Physician, Erasmus Wilson (5,6). It is a persistent inflammatory (6), autoimmune disease, that affects the skin, nails, and scalp as well as the oral, nasal, laryngeal, esophageal, anal, and genital mucosae (35).

Oral Lichen Planus (OLP) consists of a non-infectious, long-term disease, withthe involvement of the oral mucosa, more specifically the stratified squamous epithelium and the subjacent lamina propria (7). It is an autoimmune pathology per TCD8+ cells, macrophages, and Langerhans's cells that can be activated due to innumerable etiological factors and lead to programmed cell death in the basal cells of the oral epithelium (5,8, 36).

OLP is characterized by alternating periods of remission and exacerbation that can endure for lasting periods, which undergoes a period of remission naturally (8,9,14). The period of exacerbation is marked by a growth of the symptoms and clinical signs (6).

There is a strong possibility that OLP can develop into a malignant form named Oral Squamous Cell Carcinoma (SCC) identified by the WHO, with the likelihood of 5.3% of OLP patients developing Oral SCC, for a period betwixt half a year to up to 20 years, with a higher incidence in erythematous and erosive form (7,9,37,38).

The etiology of the OLP is uncertain. However, some risk factors are being the target investigated which may have a part in the pathogenesis of this disease, such as:

Genetic Factors – Studies have demonstrated but not consistently that genetic polymorphisms in the cytokines like the first INF-gamma and the TNF- α have a role in the development of OLP (6);

Physiological Factors - Patients with OLP demonstrated to have higher levels of anxiety, along with elevated cortisol levels in the saliva. However, the question remains if this factor is an etiology to this disease or may contribute only to the morbidity (6);

Trauma – It is not an etiology factor, but it seems to be a process where other etiological factors may exercise their effects known as the Koebner Phenomenon (6,39,40);

Viral Infections – There has been an association between OLP and other viral infections such as CMV, HSV-1, HHV-6, EBV, HBV, and HPV (7). Various studies suggest a strong association between HCV with a higher prevalence, more specifically 0.5 to 35 % in the Mediterranean countries, Japan, and the United States of America (6,8,36). Some studies suggest that this can occur due to an increase of HLA class II allele HLA-DR6, which may elucidate the geography diverseness (6). These may be due to the capacity of the HCV virus to clone itself in non-hepatocyte cell types and the extreme capacity of mutability (35);

Systemic Diseases – There has been an association between OLP and major systemic diseases such as hypertension, diabetes mellitus, thyroid dysfunction, hypothyroidism, Hashimoto thyroiditis, dyslipidemia, and bowel diseases such as celiac disease, ulcerative colitis, and Crohn's disease (6,8). Also, it can be associated with autoimmune disorders such as Systemic Lupus Erythematosus, Sjögren syndrome, and others (7);

Systemic Medication – Some medicines like beta-blockers, non-steroid anti-inflammatory, antimalarials, diuretics, oral hypoglycemic, and oral retroviral medication can begin or aggravate the OLP (5,41,42,43,44).

3.1.1. Epidemiology

The incidence in the general society is 0,5 % to 2,2 % (35), with an occurrence higher in females than in men (ratio of 2 to 1). It is more predominantly in the 30 to 60 years (9) and senior people (37). Although, it is infrequent in infants and adolescents (45). Additionally, OLP does not prefer races (9).

3.1.2. Clinical Manifestations

According to the classification of Andreasen, six OLP subtypes can be individually or, most commonly, be a combination of various as illustrated in Figure 2 (6,35):

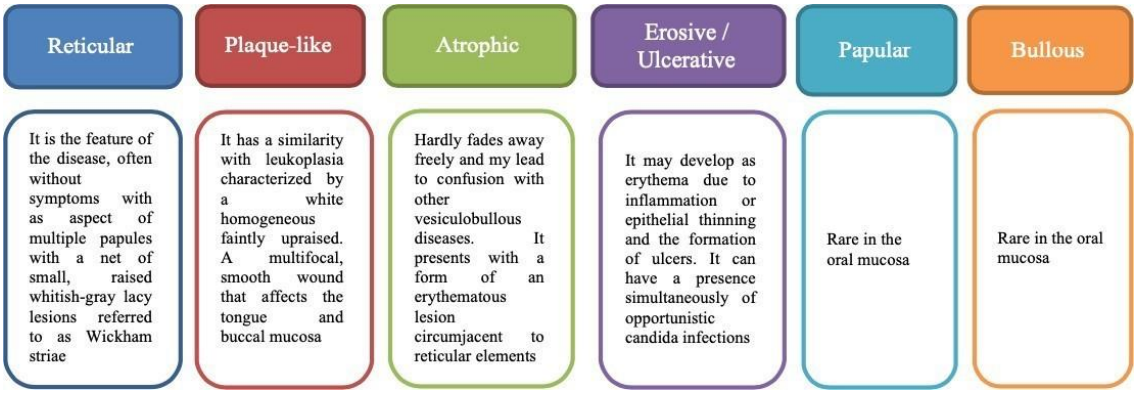


Figure 2 - Subtypes of Oral Lichen Planus (8,35,38)

These signals and symptoms of OLP can affect all parts of the oral cavity, with a higher incidence in the oral mucosa (7,35). The ensuing locals are the lingual, gingival, and labial mucosa. These clinical features symmetrically and bilaterally diffuse in posterior regions as shown in Figure 3 (35).

Alongside the signals and symptoms in the oral mucosa, patients have also described roughness in the mouth, sensitivity to hot or spicy nourishments, pain in the oral mucosa, ulcers in the mouth, flaming sensation, enlargement, and mucosal hemorrhage in some activities such as brushing the teeth (6, 46).

OLP can also be the manifestation of other symptoms besides the mouth, namely the genital mucosa, with a probability of 20% in females with OLP and lesions in the skin that affects 15% of people with OLP (9).

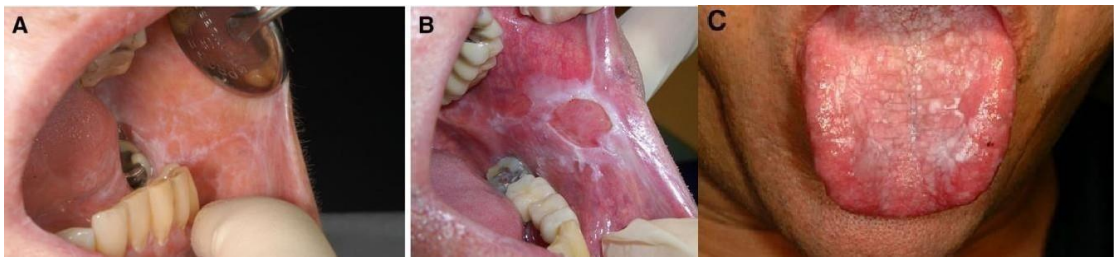


Figure 3 - Clinical Manifestations of OLP (A - Reticular; B - Erosive; C - Atrophic andPlaque-like (6)

3.2. Pemphigus Vulgaris

The term "Pemphigus" derivates from the Greek word "pemphix" known as blister or bubble, which leads to excess mortality and morbidity, used, firstly, by Hippocrates from 460 to 370 B.C (47,48,49). It is a long-term, possibly deadly autoimmune disease of the stratified squamous epithelia (11,47,49). The observed production of IgG autobodies reacts in the keratinocytes, resulting in acantholysis (absence of adherence between the keratinocyte's cells) (47).

The IgG autoantibodies go straight to the desmosomes (Dg1 and Dg3) and other protein components of the composition of the mucous membranes like the desmocollins and plakins (12,49). The desmosomes are part of the family of cadherins with the function of sustaining the structure of the stratified squamous epithelia (10). Although, others can be detected such as IgM, IgA, and C3 (11).

In addition, numerous factors may trigger this disease such as genetic factors that explain the higher incidence in certain populations. Also, there are extrinsic factors like drugs, viruses, allergens, dietary factors, emotional stress, pregnancy, change in hormones, radiotherapy, UV radiation and sun exposure, seasons, or other environmental factors (11,50).

3.2.1. Epidemiology

The incidence differs according to the country (51). Therefore, some studies demonstrate that the prevalence can be 1 to five cases per million yearly (10). However, it has a higher incidence in the Jewish population, which may be due to genetic or other factors that may provoke this disease, especially between the Mediterranean, Indian, Malaysian, Chinese, and Japanese populations (11,13).

Additionally, from the Pemphigus family, PV is the most prevalent in European countries, the United States of America, and Japan, with a higher frequency in females and mid-age people (38). It is key to highlight that some causes in children have been seen (12). In addition, in European countries, the prevalence of PV varies indirectly with the latitude (38).

3.2.2. Clinical Manifestations

As shown in Figure 4, the lesions appear on the skin, and then after a few months emerge in the mouth. It begins with blisters that effortlessly burst to lead to erosions and ulcers (10, 14). These can be restricted to the area for up to 1 year and then extended to all body, leading to a burning sensation, debility discomfort, nose bleeding, weight loss, dysphagia, and hoarseness (12).

These lesions can occur in the gingiva, buccal or palatal mucosa, but can influence other locations such as conjunctiva, esophagus, pharynx, larynx, urethra, penis, labia, vagina, cervix, and anus mucosae (12).

There can be three subvariants: mucosal-only disease, which only prevails the anti-Dsg3 autoantibodies; cutaneous-only disease, where there is a predominance of the anti-Dsg1 autoantibodies; and the one who is more common, mucocutaneous where there is an existence of the anti-Dsg1 and anti-Dsg3 autoantibodies (51). These subtypes may be explained by the desmoglein compensatory theory (52).

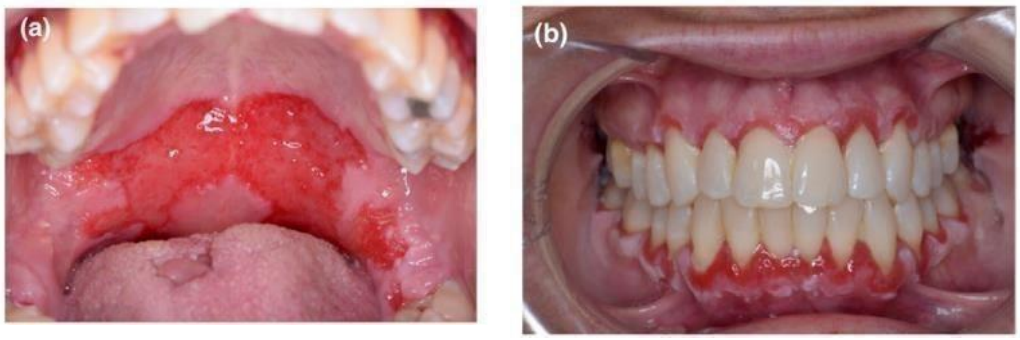


Figure 4 - Clinical Manifestations of Pemphigus Vulgaris (16)

3.3. Mucous Membrane Pemphigoid

Mucous Membrane Pemphigoid (MMP) also designated cicatricial pemphigoid is an infrequent, long-standing, and autoimmune disease that describes causing subepithelial blisters on distinct mucous membranes: oral, nasal, laryngeal- esophageal, genital, and conjunctival mucosa and with a less frequency in the skin (13,15,53,54,55).

Additionally, it presents with a slow outset with alternative periods, periods where there is a heightening or a lessening of the signals and symptoms of this disease (16).

It has been reported that there is a connection between the IgG, IgA, and C3 to various components of the BMZ, more specifically the hemidesmosomes such as BP-180, laminin 332 (laminin 5), p200, type VIII collagen, and $\alpha 6\beta 4$ integrin, which leads to inflammation and fragility in the epidermis 2,15,17,49,56)

3.3.1. Epidemiology

The incidence is variable depending on the country. However, aging people are predominant, in the middle of 60 to 80 years, with a slight preference for women (15,57). Additionally, it has no racial or geographic predisposition (56).

3.3.2. Clinical Manifestations

It is important to be aware that clinically the MMP and the PV are indistinguishable (13).

Some studies mention that the appearance of these signals is a formation of erythematous patches, blisters, or even erosions (16). Consequently, it quickly ruptures leading to pain in these asymmetrical erosions or ulcers with yellowish slough encircling by an erythematous halo (13,15). Therefore, this can result in dysphagia, soreness, fetor, hemorrhage, and or peeling of the mucosa (15). This can be illustrated in Figure 5.

The predilection of the onset of this disease is the oral cavity (15). However, that can extend to other places, some more frequent than others: the ocular, nasal anogenital, pharyngeal, laryngeal, and esophageal mucosae (15).

It is important to highlight that skin can be affected, yet on a less scale than the other mucocutaneous autoimmune diseases (15). The signals and the symptoms exclusively of the oral cavity that features this disease, from the most to the least frequent local are the gingivae, buccal mucosa, palate, tongue, and the lower lip (16).

There are some consequences due to these signals and symptoms such as diminished visual acuity, vision loss, supraglottic stenosis with hoarseness, and a blockage of the airway (56).

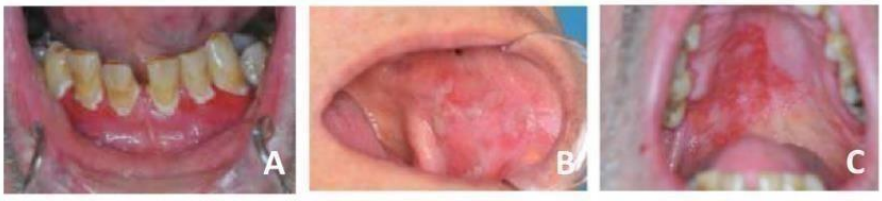


Figure 5 - Clinical Manifestations of Mucous Membrane Pemphigoid (A – gingivae, B –Buccal mucosa, C – palate) (3)

A summary of the pathology definition, epidemiology, signals, and symptoms, physiopathology, and diagnosis of the three pathologies is shown in Table 1.

Table 1 - Summary of the Pathologies Oral Lichen Planus, Pemphigus Vulgaris, and Mucous Membrane Pemphigoid (5-20)

Pathology	Definition	Epidemiology	Signals and Symptoms	Physiopathology	Diagnostic	Bibliographic References
Oral Lichen Planus	An autoimmune, non-transmissible, chronic inflammatory and non-remissive disease may cause morbidity. Also, it has a higher probability to be upgraded into a malignant form, with no spontaneous resolution, activated by various etiological agents. It affects the oral mucosal stratified squamous epithelium and the underlying lamina propria and may cause skin lesions. It is characteristic of this disease to have alternating periods of remission and exacerbation, set off by psychological or physical stress, chronic mechanical trauma, and the ingesting of irritative foods and refreshments	A conjecture about the prevalence is a ratio of 0.5 to 3% in the general population, with a higher incidence in females and ages between 30 to 60 years, although all group ages are affected, without a preference of races	Bilateral, symmetrical patterns in the oral mucosa, may affect other areas such as the tongue, gingiva, and labial mucosa. These lesions are principally in the posterior regions of the mouth. Some patients tell roughness in the tongue, sensibility to hot or spicy food, pain, and red or white patches or ulcerations in the oral mucosa. The trademark of this disease is a Wickham's striae, on the top of the lesion, with fine grayish-white lines	Although the whole mechanism is not known, studies suggest that by being OLP an autoimmune disease is mediated by T CD 8+ cells, macrophages, and Langerhans's cells. Therefore, this mechanism provokes apoptosis, consequently causing cell destruction and the presence of the features in the histological examinations of OLP	Clinical and histological examinations are characterized by infiltrations of lymphocytes in the connective tissue zone, an appearance of an epithelial basal layer liquefaction degeneration, no existence of atypia or epithelial dysplasia, and overlying keratinization. It can also be detected by direct immunofluorescence (DIF) and indirect immunofluorescence (IF)	5-20

Table 1 – Summary of the Pathologies of Oral Lichen Planus, Pemphigus Vulgaris and Mucous Membrane Pemphigoid (5-20) (cont.)

Pathology	Definition	Epidemiology	Signals and Symptoms	Physiopathology	Diagnostic	Bibliographic References
Pemphigus Vulgaris	An autoimmune, chronic disease of stratified squamous epithelia that causes acantholysis and intraepithelial blistering. It begins in the oral cavity, that may progress to the skin in the forthcoming months	Overall, it presents in the ages betwixt 40 and 65 years in most of the world. Also, it has a higher prevalence in women. The extent is one to five million cases every year, that is 0,1 to 0,5 in 100 000 population, with a high rise in some ethnic groups such as Ashkenazi Jewish, Mediterranean, Indian, Malaysian, Chinese, and Japanese population	It begins in the oral cavity, with an enanthema and erosions, predominantly in the buccal mucosa, tongue, palate, and inner side of the lips. Pain is changeable from a slight ache to not ingesting food, resulting in speedy weight reduction. The first are flaccid blisters that evolve to the erosions and ulcers duo to simply bursting, consequently originating serious deathly infections and metabolic abnormalities. Also, the lesions are poorly defined, irregular, and located, thus leading to a sensation of burning, epistaxis, malaise, dysphagia and hoarseness	Occurs the production of IgG autoantibodies that connect against the desmogleins, Dsg1, and Dsg3, responsible for the cell adhesion leading to a separation of the adjacent keratinocytes, known as acantholysis. The autoimmune reaction occurs due to autoreactive T and B lymphocytes. The existence of the blisters occurs due to an increment of secretion of pro-inflammatory mediators	Based on clinical manifestations, alongside immunological and histological tests. The direct immunofluorescence detects an accumulation of IgG or C3 with a honeycomb-like pattern in the keratinocytes cell's membrane. Also, the ELISA identifies in the serum anti-Dsg1 or Dsg3 autoantibodies, being beneficial for diagnostic and monitorization. The confocal laser scanning microscopy is helpful to keep track of this disease and the efficacy of the treatment. The histological tests reveal the presence of acantholysis, remaining a row of the basal keratinocytes, with an aspect like a row of tombstones or tombstoning and a scanty inflammatory infiltrate	5-20

Table 1 – Summary of the Pathologies of Oral Lichen Planus, Pemphigus Vulgaris and Mucous Membrane Pemphigoid (5-20) (cont.)

Pathology	Definition	Epidemiology	Signals and Symptoms	Physiopathology	Diagnostic	Bibliographic References
Mucous Membrane Pemphigoid	An uncommon autoimmune disease, predominately in the mucosa subepidermal causing blisters in the oral mucosa, conjunctiva tissues, and upper aerodigestive tract. It has a progressive pack with mixed periods of exacerbations and remissions. However, the significant sites of involvement in this disease is in the oral and conjunctival mucosae.	Generally, it affects midlife and seniority, with a preference for the Caucasian race. It has a prevalence of 2 million people per year. It also has a higher incidence in women than in men.	It occurs with the formation of blisters with different proportions, varying from minuscule to sizeable vesicles and bullae. It affects the oral cavity, namely the buccal mucosa, soft palate, lips, and gingiva. The last epithelial tissue' causes desquamative gingivitis, provoking patches or extensive erythema. Also, it can cause hemorrhagic bullae, transforming into breakage, resulting in irregularly shaped erosions and ulcers with a yellowish shed encircling by an erythematous halo. It may also lead to pain, dysphagia, soreness, fetor, and peeling of the mucosa	It characterizes by a straight build-up of autoantibodies (IgG, IgA, or C3) in the basement membrane zone, more specifically, in the mucosal and epithelial membrane zones to connect with a variety of antigens: the type XVII and VII collagen alongside the laminin 332 and the BP- 180	It bases on clinical presentation and histological and immunological tests. The histological test has a subepithelial split with mixed inflammatory infiltrates, namely eosinophils, lymphocytes, and neutrophils. The prevailing is positive direct immunofluorescence (DIF) for IgG, IgA, IgM, or C3 at the basal membrane zone	5-20

4. Corticosteroid Therapy

4.1. Introduction

Corticosteroids, also designated as steroids, consist of manufactured medicine used in numerous specialties (58). The fundamental action of corticosteroids is to decrease inflammation and overpower the immunity system (30). Therefore, various diseases are being treated with this medicine like respiratory (asthma and chronic obstructive pulmonary disease), allergic (allergic rhinitis and hives), dermatological (atopic eczema), and autoimmune diseases, for instance, the Inflammatory Bowel Disease (IBD) (Crohn's disease and ulcerative colitis), Multiple Sclerosis, lupus, rheumatoid arthritis, and of course the OLP, PV and MMP (30).

They bear a resemblance to cortisol, a hormone produced by our body, more specifically by the adrenal glands, through the cholesterol pathway (58,59). Cortisol, an endogenous glucocorticoid has a prime effect on our organism since it participates in several biological processes such as glucose metabolism, immunity system, and stress (58,59).

A flawless topical corticosteroid must be efficacious at the site of application but with no or subsidiary side effects (60). Therefore, countless features influence the inherence power of the medicine, the sort of vehicle used, the regularity of application, the membrane characteristics, and the aptness of skin penetration with a suitable skin concentration but with low concentrations in the blood concentration (61-63).

4.2. History

In 1948, Kendall discovered several compounds belonging to the adrenal glands of bovines, which were given the alphabet letters, A to F (27). In the middle of these, there were the elements E, cortisone, and the element F, hydrocortisone, which are helpful in human pathologies (27).

In the year 1952, Witten and Sulzberger, hydrocortisone was found to be effective topically in dermatological effects, whereas cortisone does not affect skin disorders (28,29).

4.3. Structure

Hydrocortisone is the first compound discovered with multiple potentialities (64). Therefore, it is the foundation of the structure of a variety of corticosteroids (65). In addition, it is composed of 21 atoms of carbon with a nucleus, cyclo-pentano- perhydro-phenanthrene, which is nominated from A to D, where are three rings with six carbon atoms and one ring with five carbon atoms and with a pendant chain designated for 17, 21- dihydroxy (OH-20-keto (O)) (28,64,65,66,67). The various side chains are responsible for glucocorticoid activity (56). All the mentioned above are illustrated in figure 6.

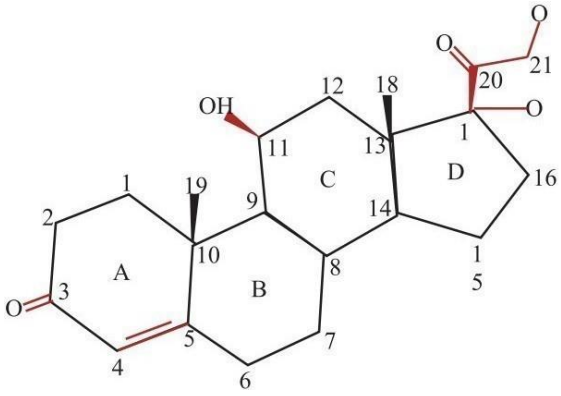


Figure 6 - Structure of the Hydrocortisone Molecule (28)

However, several modifications were made that can help maximize the clinical benefits and minimize the adverse effects (28) like:

- The introduction of fluorine to the compound by the electrophilic at the C6 and C9 atoms causes a rise in efficacy (64). In the C9, it also can cause a lessening of the mineralocorticoid activity (28);
- The simultaneous existence of a double bound between C4 and C5 and a ketone group gives both glucocorticoid and mineralocorticoid activity (68);
- The establishment of an acetonide group in the C16 and C17 atoms (28) amplifies the penetrability and percutaneous absorption (64);
- Substitution between the hydrogen atoms for halogen atoms at the C9 or C6 or both these atoms leads to a climb in the potency (64) because of an augmentation of the link with the glucocorticoid receptor (67). Also, it has the disadvantage of intensifying the effects of mineralocorticoid activity (61);

- The introduction of a secondary fluoride or a chloride group also leads to a rise in efficiency (65);
- The introduction of a double bond between the C1 and C2 positions escalates the glucocorticoid activity (65) and the anti-inflammatory activity (69) with a decline in the metabolism rate (65);
- The elimination or masking of the 17-hydroxyl acetone side chain or the 16-!-hydroxyl group intensifies the lipophilicity (70);
- The introduction of an ester (esterification) at the C17 and C21 improves the lipophilicity and a superior penetrability of the skin (71);
- To minimize the effects of the mineralocorticoid activity, it can be arranged by the addition of 16-α-methyl, 16-β-methyl, or 16-α-hydroxyl groups (72).

4.4. Topical Corticosteroids: classification

The WHO classifies corticosteroids into seven groups, from the most to the least powerful (10) (Table 2). This powerfulness is characterized by the activity of the molecule, the concentration, and the essence of the vehicle (73). Therefore, the seven groups of corticosteroids are graded into four classes of potency: Class I – Ultra high potency; Classes II and III – High Potency; Classes IV and V – Moderate Potency and Classes VI and VII -Low Potency (28).

However, the BNF fractionates into four groups, where class I is extremely potent, and class IV has a shallow potency (66), where the sort of vehicle is not considered (74).

Nevertheless, the prominent potency is accompanied by a substantial therapeutical effect, but also with a considerable amount of side effects (75).

Table 2 - Classification of Topical Corticosteroids according to the WHO Classification (28,76)

POTENCY	CLASS	CORTICOSTEROID	FORMULATION	CONCENTRATION (%)
Ultrahigh	I	Clobetasol propionate	Cream	0.050
		Diflorasone diacetate	Ointment	0.050
		Diflucortolone valerate	Ointment, Cream	0.30
		Betamethasone dipropionate	Ointment, Cream	0.050
		Halobetasol propionate	Ointment, Cream	0.50

Table 2 - Classification of Topical Corticosteroids according to the WHO Classification **(**28, 76**)** (cont.).

POTENCY	CLASS	CORTICOSTEROID	FORMULATION	CONCENTRATION (%)
High	II	Amcinonide	Cream	0.010
		Betamethasone dipropionate	Ointment	0.050
		Desoximetasone dipropionate	Ointment, Cream	0.025
		Fluocinonide	Ointment, Cream, Gel	0.050
		Halcinonide	Cream	0.100
		Diflorasone diacetate	Ointment	0.500
		Mometasone furoate	Ointment	0.100
		Triamcinolone acetonide	Ointment	0.500
	III	Betamethasone dipropionate	Cream	0.050
		Betamethasone valerate	Ointment	0.100
		Diflorasone acetate	Cream	0.050
		Triamcinolone acetonide	Ointment	0.100
		Amcinonide	Cream, Lotion	0.100
		Fluticasone propionate	Ointment	0.050
		Fluocortolone	Cream	0.250
		Fluocinonide	Cream	0.050
		Halcinonide	Ointment	0.100
		Triamcinolone acetonide	Cream	0.500

POTENCY	CLASS	CORTICOSTEROID	FORMULATION	CONCENTRATION (%)
Moderate	IV	Desoximetasone	Cream, Gel	0.050
		Fluocinolone acetonide	Ointment	0.025
		Fludroxycortide	Cream	0.050
		Hydrocortisone butyrate	Cream	0.100

Table 2 - Classification of Topical Corticosteroids according to the WHO Classification **(**28, 76**)** (cont.).

POTENCY	CLASS	CORTICOSTEROID	FORMULATION	CONCENTRATION (%)
Moderate	IV	Hydrocortisone Valerate	Cream, Ointment	0.200
		Triamcinolone acetonide	Lotion, Cream	0.100
		Betamethasone valerate	Lotion	0.010
		Fluocinolone acetonide	Cream	0.200
		Flurandrenolide	Ointment	0.050
		Halcinonide	Cream	0.025
		Mometasone furoate	Cream	0.100
	V	Betamethasone dipropionate	Lotion	0.020
		Betamethasone valerate	Cream	0.100
		Fludroxycortide	Cream	0.050
		Hydrocortisone butyrate	Cream	0.100
		Hydrocortisone valerate	Cream	0.100
		Triamcinolone acetonide	Lotion	0.100
		Betamethasone dipropionate	Lotion	0.050
		Fluocinolone acetonide	Oil	0.010
		Flurandrenolide	Cream	0.050
		Fluticasone propionate	Cream	0.050
		Fluocinolone acetonide	Cream	0.050
		Hydrocortisone valerate	Cream	0.200

POTENCY	CLASS	CORTICOSTEROID	FORMULATION	CONCENTRATION (%)
Low	VI	Betamethasone valerate	Lotion	0.050
		Desonide	Cream	0.050

Table 2 - Classification of Topical Corticosteroids according to the WHO Classification **(**28, 76**)** (cont.).

POTENCY	CLASS	CORTICOSTEROID	FORMULATION	CONCENTRATION (%)
Low	VI	Fluocinolone acetonide	Solution, Cream	0.010
		Alclometasone dipropionate	Ointment, Cream	0.050
		Prednicarbate	Cream	0.100
		Triamcinolone acetonide	Cream	0.100
	VII	Dexamethasone sodium phosphate	Cream	0.100
		Hydrocortisone acetate	Cream	1.000
		Methylprednisolone acetate	Cream	0.250
		Hydrocortisone	Ointment, Cream	0.500
		Hydrocortisone	Ointment, Cream	2.500

** The corticosteroids that present the grey color there are simultaneous in both categories accordingly to multiple bibliography references.

4.5. Mechanism of Action

The mechanism of action occurs due to glucocorticoid receptors as illustrated in Figure 7 (64). These are widespread throughout the body (69,70). In the skin, they are present in the dermis and epidermis, more specifically in the fibroblasts and keratinocytes) (77,78).

When the receptor is not bounding with the corticosteroid, it is classified as inoperative (68). It localizes in the cytoplasm or the exterior of the nuclear membrane (68, 69) and joins with multiple proteins such as Hsp (Heat-shock proteins) like Hsp90, Hsp70, and immunophilins (28).

However, when the corticosteroid molecule, being lipophilic, enters the organism, passes to the cell by passive diffusion (60). In the cell, the molecule connects to the receptor, and the proteins mentioned above detach (28,29). Therefore, occurs the

formation of the complex between the glucocorticoid-receptor that resettles in the nucleus (28).

Whereas, in the nucleus, the complex reference in the previous paragraph links to a particular sequence of DNA (69) designated by GRE (28). Consequently, it causes the synthesis of anti-inflammatory proteins such as AP1, NFKB, and IRF-3 regulatory proteins that play a role in metabolic processes (79).

Also, it can oversee the synthesis of pro-inflammatory mediators such as macrophages, eosinophils, lymphocytes, mast cells, and dendritic cells, inhibits the phospholipases A2, in charge of various inflammatory mediators, obstructs the genes that assure the expression of cyclooxygenase-2 and impedes the upregulation of lipocortin and annexin A1 (59).

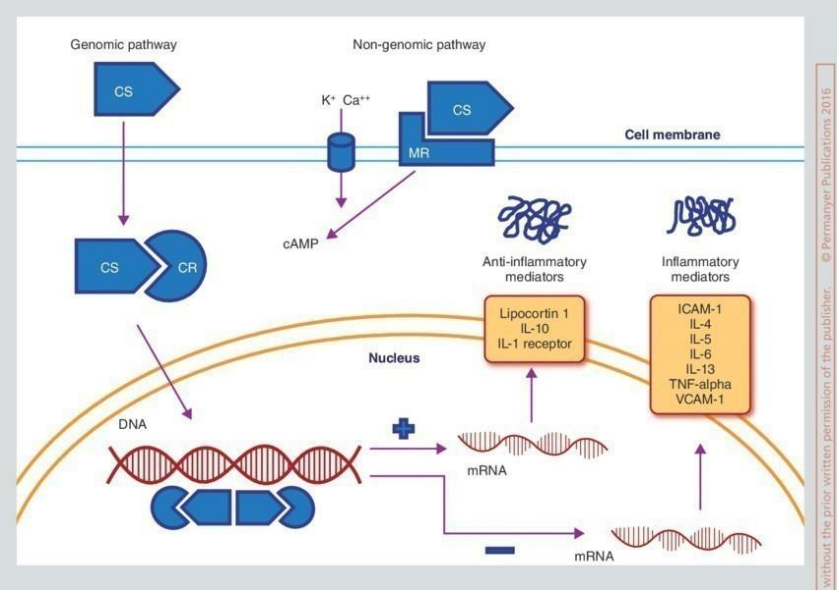


Figure 7 - Mechanism of action of corticosteroids with the anti-inflammatory function(transaction, transrepression) (80)

However, it is important to refer that besides the anti-inflammatory activity, the corticosteroids for mechanisms misunderstood also have:

- A **vasoconstriction action** may be due to an impediment in the performance of vasodilators such as histamine and bradykinin, which may influence the anti-inflammatory activity (81).

- An **anti-proliferative action**, where occurs a decrease in the epidermis, with the consequence of a reduced thickness of the basal cell layer (82). It also implies a diminish in the production of melanocytes (82). It also occurs atrophy because of a suppression of the production of fibroblasts, protein synthesis, collagen, and glycosaminoglycans (28,63).

4.6. Choice of Topical Corticosteroid, Application Technique, Frequency, and Duration

Firstly, the primary question is to choose the corticosteroid that is most adequate among the variety that exists. Therefore, several factors allow an ideal choice for that clinical situation. In situations that are exceedingly reactive to this type of medicine normally is used low to moderate potency topical corticosteroids (28).

However, in situations that are not as sensitive, it should be tried higher topical corticosteroids without or with a lack of occlusion (29). In addition, in unresponsive situations, must be used super potent topical corticosteroids or chosen a different pharmaceutical form such as intralesional corticosteroids (29).

Secondly, another crucial point that should be pondered on consists of the location where the disease is localized. Consequently, areas with a thicker stratum corneum, like palms and soles, need a powerful topical corticosteroid (29). However, areas with a slimmer stratum corneum, such as the face, scrotum, and intertriginous areas require a minor potency of topical corticosteroids (28). In addition, mild efficacy of corticosteroids is preferable in areas such as the face, groin, axillae, genital, and perineal places (83).

Another strategy in therapy with this type of medicine could be the use of the occlusive dressing, which can rise penetrability (28). However, at this moment, their use is exceptional due to the existence of immensely potent corticosteroids, since they can cause severe adverse effects such as retentiveness perspiration, infections and a higher endanger of having systemic effects (28,84). Nevertheless, the areas where it can be used in the palms and soles, which are due to minor absorption and stress-bearing areas (83).

Third, the type of vehicle that is most suitable not only for the clinical conditions but also for the patient itself. Therefore, it depends on numerous factors like:

- **Pharmaceutical characteristics** (Solubility of the active substance in the pharmaceutical form, the release rate of the active substance of the vehicle; the capacity not only to hydrate the skin but also to achieve the acceptable dosages to perform their therapeutical action; the physic and chemical among the active substance and the excipients and the efficacy of the corticosteroid) (75);

- **Clinical characteristics** (Stage of the disease, the location, proportions of the disease, and the sensitivity of the disease to the treatment and the age of the patient) (75).

Another significant point in using corticosteroids is the period of treatment. Consequently, when powerful topical corticosteroids are prescribed like clobetasol propionate, the total of days of use should not exceed 14 to 20 days or cannot be used in a continuous form, and a quantity of 60 grams each week (75,83). Also, occlusion in this class of corticosteroids must be forbidden (75).

Also, one more aspect is the regularity of the application of the drug. Studies have shown that daily use has the same outcome as twice per day (79). The advantages of a daily application consist in decreasing the side effects and not affecting the prognostic of the disease itself and, a major upper hand is to ascend the compliance of the patients (63). Other studies were made between once daily and three times per day, and it demonstrates that the beginning of the clinical effects is faster if three times per day is done, but the efficacy following three weeks is the same (61). However, the culmination shows that a daily application is more convenient due to problems with the day-to-day use problems with corticosteroids, the adverse effects, and the lack of compliance of the patient to the course of treatment (61).

Furthermore, there is not an internationally recognizable recommendation that the prescribers must follow, but a common convention is to change from corticosteroids of a higher to a low efficacy or even formulations without steroids if the therapy needs to perpetuate for more than two weeks (75).

4.7. Delivery Vehicles

There are innumerable pharmaceutical forms or vehicles ranging from solid pharmaceutical forms (tablets and capsules), semi-solid pharmaceutical forms (ointments, cream, lotions, gels/hydrogels), liquid pharmaceutical forms (solutions, shampoo, and foam), and sterile pharmaceutical forms (injectable and collyrium) (64).

It is important to refer that the function of the vehicle, which is composed of one or more excipients, is to be the mean of transportation to the active substance (64). Also, the choice of vehicle depends on numerous factors such as the interlinkage between the vehicle, the skin and drug molecule, the stability, the release flow and solubility of the vehicle, the area of the body where the disease spreads (64), and most importantly, the compliance of the patient.

Creams consist of a water-based pharmaceutical form with the advantage of outspreading effortlessly in the absence of the sensation of oil, with a higher predisposition by the patients (28). However, it has the downside of reducing the hydration in the skin (63). They are applicable throughout the body but have a better outcome for hairy, intertriginous, and moist areas (28,29).

Ointments enlarge the hydration of the skin and bring an acceptable occlusion (28). They do not have water among their constituents (86). Consequently, they make an occlusive layer that contains water (78). Therefore, the after-effect boosts the percutaneous penetration and upgrades the potency (28,63). It can be administered in areas with thick skin like the palms and soles (28). However, it must be kept away from intertriginous areas (28). Also, among the several types of ointments, fatty ointments have better efficacy in their occlusion capacity and may enhance a better penetration of the profound layers of the skin (62).

Lotions consist of emulsions based on oil-in-water that have great compliance by the patients since they are unchallengingly applicable (28). Therefore, they are preferably used in scalp wounds (28), sizeable surface areas, and in the creases and folds of the body (29).

Gels are constituted by a gelling compound and offer a considerable facility in administration (28). Also, they are not greasy nor occlusive but have the drawback of

causing some adverse effects such as stinging and irritation (29). Therefore, they are more helpful in bushy areas and the face since it only remains a slight residue (29).

There can be also solutions, which are alcohol-based pharmaceutical forms and are beneficial in hair-covered areas and intertriginous areas (87).

In the last decades, there has been the development of brand-new formulations like foams and shampoo being handy in scalp lesions (87).

After underlying the advantages or disadvantages among the most used corticosteroids for the treatment of these autoimmune mucocutaneous diseases, it is prime to know their definitions and their characteristics in table 3 and illustrated in Figure 8:

Table 3 - Definition of the Semi-Solid Pharmaceutical Forms (88)

PHARMACEUTICAL FORM	GENERAL DEFINITION	SPECIFICATIONS
Ointments	" A suspension or emulsion semisolid dosage form that contains < 20 % water and volatiles and > 50 % of hydrocarbons, waxes or polyethylene glycols as the vehicle for external application to the skin"	" Contains < 20 % water and volatiles and > 50 % of hydrocarbons, waxes, or polyethylene glycols as the vehicle"
		" Opaque or translucent, viscous, greasy; tend not to evaporate or be absorbed when rubbed onto the skin"

Table 3 - Definition of the Semi-Solid Pharmaceutical Forms (88) (cont.)

PHARMACEUTICAL FORM	GENERAL DEFINITION	SPECIFICATIONS
Creams	" An emulsion semisolid dosage form that contains > 20 % water and volatiles and/or hydrocarbons, waxes or polyethylene glycols as the vehicle for external application to the skin"	" Contains > 20 % water and volatiles and/or < 50 % of hydrocarbons, waxes, or polyethylene glycols as the vehicle. These are two types of creams: an oil-water cream with water as the continuous phase and a water-in-oil with oil as the continuous phase"
		"Opaque or translucent, viscous, non-greasy to mildly greasy, tends to mostly evaporate or be absorbed when rubbed onto the skin"
Gels	" A semisolid dosage form that contains a gelling agent to provide stiffness to a solution or colloidal dispersion for external application to the skim. A gel may contain suspended particles"	"Usually contains an aqueous or alcoholic vehicle and a gelling agent such ass starch, cellulose derivates, carbomers, magnesium-aluminum, silicates, xanthan gum, colloidal silica, aluminum or zinc soaps"
		"Usually clear or translucent in a single-phase system; otherwise; opaque a two-phase system; thick, non-greasy; provides a colling sensation when applied to the skin"

Table 3 - Definition of the Semi-Solid Pharmaceutical Forms (88) (cont.)

PHARMACEUTICAL FORM	GENERAL DEFINITION	SPECIFICATIONS
Lotion	" An emulsion liquid dosage from for external application to the skin"	" Usually contains an aqueous vehicle and > 50 % water and volatiles"
		"Opaque, thin, non-greasy; tends to evaporate rapidly, with a cooling sensation when rubbed onto the skin"

Figure 8 -Topical Pharmaceutical Forms (A – Ointment, B – Cream, C – Gels, D – Foams, E –Lotion) (89-93)

4.8. Adverse Effects

Topical corticosteroids have two types of side effects: the local side effects, which are more common (94-97), and systemic, which endanger the health of the patient (94-97).

Nevertheless, to reduce the side effects of this type of drug, some measures can be down such as decreasing the potency of the corticosteroid medicine in some sensitive populations like children and geriatrics (94-97). Also, other ways are to subside the dosage or to diminish the regularity of application (94-97).

4.8.1. Local Adverse Effects

As seen in the mechanism of action of the corticosteroids, it could interfere with the synthesis of collagen and the processes connected to wound healing (94-97). In addition, there is also an increment in a predisposition to infections (94-97).

Consequently, the dermatological side effects are due to the facts mentioned above and are summarized in Table 4.

Table 4 - Dermatological Side Effects of the Use of Corticosteroids (28,61,62,63,65,69,72,76,98)

Telangiectasias	Rosacea	Allergic Contact Dermatitis
Ulcerations	Hypertrichosis	Perioral dermatitis
Slow wound healing	Alopecia	Contact Urticaria
Striae distensions	Candidiasis	Granuloma Gluteal Infantum
Bateman's Purpura	Tinea Incognito	Hypopigmentation
Facile bruising	Herpes Incognito	Exacerbate ou cover up infections
Stellate scares	Impetigo Incognito	Epidermal Thinning
Steroid Induce Acne	Demodicidiosis	Erythema
Skin Atrophy	Eczema Craquelé	Xeroderma

Table 4 – Dermatological Side Effects of the Use of Corticosteroids (28,61,62,63,65,69,72,76,98) (cont.)

Flush	Star-shaped False Scar	Erythrosis interfollicullariscoli
Cutis linearis punctata colli	Elastofibroma	Millia
Colloid millia	Poikiloderma-like change	Photosensitivity
Pustule		

4.8.2. Systemic Adverse Effects

Beyond the local adverse effects, there can also occur systemic effects. This may be due to the use of super potent potency of corticosteroids, the dosages, the frequency, the prolonged use of corticosteroids, and the clearance of this medicine(27,28,63). These systemic consequences are due to absorption through the skin, and it must maintain in a certain quantity in the organism for some time (28,60,72).

One of the most frequent is repression of the hypothalamo – pituitary-adrenal axis which may lead to the beginning or a worsening of some diseases (diabetes mellitus or hyperglycemia, due to forbidden liberty of insulin front the " cells of the pancreas, Cushing's syndrome due to the use of this medicine, repression of the adrenal gland, and mineralocorticoid consequences like edema, hypocalcemia, hypokalemia, and hypertension (60,64).

The suppression of the hypothalamo- pituitary-adrenal axis results in lower cortisol and undersupplies of the adrenal gland (69).

In addition, there can also cause osteoporosis mostly affecting the vertebras and the ribs, and AVN or osteonecrosis in grown-ups, more specifically in the femur (28,29,60. The ones who are at a greater risk of developing this adverse effect are women in menopause and aged people (60). Also, in some specific populations, like children, it can cause growth slowness due to a reduction in the levels of the GT and the hormones associated with the thyroid (60).

Also, other side effects referred to the use of corticosteroids are an increase in the body weight, a disparity of electrolytes peptic ulcer, and gastritis (63).

4.9. Contraindications

Firstly, corticosteroids should not be used if the patient has some type of allergy to the group of corticosteroids, but also to the vehicles associated with which formulation (99).

Second, if the patient has ulcerations or any type of infection (viral, bacterial, and fungal), the use of corticosteroids is inadvisable (99).

4.10. Day-to-day problems with corticosteroid use

One of the most common problems is due to duration, frequency of treatment, applied quantity, and others not only related to treatment but with the patient is known as Tachyphylaxis or Acute Tolerance (29,98). This is when some of the results of using corticosteroids are absent due to a continuous application, resulting in resistance by the organism (72).

Furthermore, another problem is the interlinkage between corticosteroids and special populations. In the pediatric population, it is preferable to use corticosteroids with low potency due to an excessive likelihood of developing adverse effects because of the extent of the surface area to body weight proportion and frail skin (100). In addition, the kidneys and the liver are not fully developed, so they are not developed enough to handle the side effects of corticosteroids (60).

In addition, aged people also have a greater susceptibility to developing adverse effects due to senescence that leads to deterioration of the skin (101). Moreover, the kidneys and the liver could not work to their fullest functions (60).

Nevertheless, to all the good that the world can extract with the use of corticosteroids, it is mandatory to educate our population about their misuse and to inform them of the correct use of this medicine.

Therefore, the healthcare professionals need to teach the quantity permitted for each week according to the FTU scale, the duration of the treatment, the exchange to corticosteroids of a lower potency in maintenance treatment, and program other

appointments when the point of treatment is not fulfilled, the side effects, and some of the precautions with the use of this drug (102).

5. Corticosteroid in Mucocutaneous Diseases of Autoimmune Cause

Corticosteroid therapy constituted a benchmark treatment of the Mucocutaneous Diseases of Autoimmune Cause, where the only difference is the route of administration.

The first line of treatment of OLP, in low to moderate, corresponds to topical corticosteroids and in severe forms, it corresponds to oral corticosteroids (21). Whereas in MMP and PV the primary treatment corresponds to oral corticosteroids, which can be adjuvant by topical corticosteroids (22-26).

According to the platform UpToDate (103-105) and the Infomed of Infarmed (National Authority of Medicines and Health Products), table 5 shows all the available corticosteroids that are prescribed for the mucocutaneous diseases of an autoimmune cause and all the possible active substances and respective pharmaceutical form most suitable to use in these three diseases that are commercialized in Portugal. It is important to know that exist other active substances in other countries but there are not available in Portugal.

Table 5 - Systemic, Systemic, and Topical and Topical Corticosteroids use in OLP, PV, and MMP (106-144)

International Common Name	Physicochemical Characteristics		Commercial name	Adverse Effects	Contraindications	Interactions	Bibliographic References
	Molecular Weight (mg/mol)	Chemical Formula	[Dosage | Pharmaceutical Form]				
Prednisolone	360.444	C21H28O5	Lepicortinolo [20 or 5 mg | Tablet]; Lepicortinolo [25 mg/1 mL | Powder and Solvent to Injectable Solution]; Prednisolona Labesfal [20 or 5 mg | Tablet];	Body fluid retention, Hypertension, Acne, Ecchymosis, Superinfection, Decreased body growth, Lipids abnormal, Muscle weakness, Osteoporosis, Headache, Cataract, Glaucoma, Raised intraocular pressure, Euphoria, Psychotic disorder, Congest heart failure, Kaposi's sarcoma, Diabetic ketoacidosis, Hyperglycemia Hypocortisolism, secondary to another disorder Iatrogenic Cushing's disease, Gastrointestinal perforation, Pancreatitis, Seizure, Pulmonary tuberculosis, Drug-induced myopathy	Systemic Fungal Infections	Rotavirus Vaccine, Desmopressin, Fluoroquinolones, Sorafenib, Bupropion, Macimorelin, Bemiparin, NSAIDS, Ceritinib, Lutetium Lu 177, Darunavir, Aldesleukin, Sargramostim, Nadroparin	104, 105,106
Methylprednisolone	374.4706	C22H30O5	Advantan [1 mg/g | Cutaneous Emulsion, Ointment, Lotion] Depo-Medrol [40 mg/1 mL or 80 mg/2 mL | Injectable Suspension]; Medrol [16 mg or 4 mg | Tablet]	Hypertension, Body fluid retention, Decreased body growth, Hypernatremia, Muscle weakness, Osteoporosis, Cataract, Congest heart failure, Sinus bradycardia, Hyperglycemia, Hypocortisolism secondary to another disorder, pancreatitis, Hepatotoxicity, Aseptic necrosis of bone, Glaucoma, Psychotic disorder, Pulmonary tuberculosis	Hypersensitivity to methylprednisolone or any component of the product, Systemic fungal infections	Rotavirus Vaccine, Desmopressin, Fluoroquinolones, Ritonavir, Voriconazole, Telaprevir, Bupropion, Macimorelin, Bemiparin, Cobicistat, NSAIDS, Lutetium Lu 177, Aldesleukin, Sargramostim, Nadroparin	107,108,109

Table 5 - Systemic, Systemic, and Topical and Topical Corticosteroids use in OLP, PV, and MMP (106-144) (cont.)

International Common Name	Physicochemical Characteristics		Commercial name	Adverse Effects	Contraindications	Interactions	Bibliographic References
	Molecular Weight (mg/mol)	Chemical Formula	[Dosage | Pharmaceutical Form]				
Dexamethasone	392.4611	C22H29FO5	Decadron [0.5 mg | Tablet]; Dexametasona Kabi MG [4 mg/mL | Injectable Solution]; Dexametasona Krka [4 or 8 or 20 mg | Tablet]; Dexametasona Krka [4 mg/mL | Injection Solution or for infusion]; Dexametasona Medsco [4 mg/mL | Injectable Solution]; Dexametasona Pharmaken [4 mg/mL | Injection Solution]; Dexaval [1 mg/g | Lotion]; Dexaval Capilar [1 mg/mL | Cutaneous Solution]; Oradexon [5 mg/mL | Injection Solution];	Hypertension, Cushing's syndrome, Decreased body growth, Abnormal vision, Cataract, Depression, Euphoria, Pulmonary tuberculosis, Cardiomyopathy, rupture of ventricle due to acute myocardial infarction, Hyperglycemia, Hypokalemia, Pancreatitis Infectious Disease, Osteoporosis, Conjunctival hemorrhage, Glaucoma, Keratitis, Retinal tear, Retinal Vascular Disorder, Uveitis	Active ou suspected ocular or periocular infection, Advanced glaucoma, Concomitant use of more than a single dose of dexamethasone with Rilviprine, Hypersensitivity to dexamethasone or any component of the product, Posterior lens capsule torn or ruptured, Systemic fungal infections	Rotavirus Vaccine, Praziquantel, Desmopressin, Artemether, Rilvipirine, Fluoroquinolones, Nirmatrelvir, Ritonavir, Fentanyl, Nifedipine, Thalidomide, Amiodarone, Dronedarone, Enzalutamide, Vincristine, Tramadol, Pentazocine, Efavirenz, Bupropion, Piperaquine, Ubrogepant, Ulipristal, Fexinidazole, Boceprevir, Darunavir, Hydrocodone, Voxilaprevir, Macimorelin, Codeine, Daclatasvir, Oxycodone, Methadone, Abametapir, Telaprevir, Bemiparin, Elvitegravir, Vortioxetine, Lapatinib, Velpatasvir, Alfentanil Sufentanil ,Buprenorphine, Meperidine, Doxorubicin, Fosamprenavir, Conivaptan, NSAIDS, Etravirine, Cholestyramine, Ceritinib, Lutetium Lu177, Tacrolimus, Nilotinib, Hemin, Dihydrocodeine, Lumateperone, Sunitinib, Fedratinib,, Nevirapine, Aldesleukin, Hormonal Contraceptives, Sargramostim, Nadroparin, Nimodipine	110,111,112

Table 5 - Systemic, Systemic, and Topical and Topical Corticosteroids use in OLP, PV, and MMP (106-144) (cont.)

International Common Name	Physicochemical Characteristics		Commercial name	Adverse Effects	Contraindications	Interactions	Bibliographic References
	Molecular Weight (mg/mol)	Chemical Formula	[Dosage | Pharmaceutical Form]				
Hydrocortisone	362.4599	C21H30O5	Locoid [1 mg/g | Lotion]; Locoid Capilar [1 mg/mL | Cutaneous Solution]; Locoid Crelo [1 mg/g| Skin Emulsion]; Locoid Lipocreme [1 mg/g | Lotion]; Carplexil MG [10 mg/g | Lotiont]; Hidrocortisona Bluepharma [10 mg/g | Lotion]; Hidrocortisona Color MG [100 mg/ 2 mL | Powder and Solvent to Injectable Solution]; Hidrocortisona Generis [100 mg | Powder to Injectable Suspension]; Pandermil [10 mg/g | Lotion, Ointment]; Solu-Cortef [100 mg/ 2 mL | Powder and Solvent to Injectable Suspension]; Hidrocortisona Roussel [10 mg | Tablet]; Hydrocortone [10 or 20 mg | Tablet];	Hypertension, Body fluid retention, Impaired glucose tolerance, Weight gain, Increased appetite, Altered behavior, Disturbance in mood, Cushing's syndrome, Growth retardation, Hyperglycemia, Pheochromocytoma, Crisis, Osteoporosis, Cataract, Glaucoma, Delirium, Depressed mood, Euphoria, Mania, Psychotic disorder, Hallucinations, Pulmonary tuberculosis	Hypersensitivity to hydrocortisone or any of its components, Systemic fungal infections, Ileocolostomy during immediate o early postoperative period	Desmopressin, Fluoroquinolones, Vaccines, Macimorelin, Lutetium Lu 177, Abametapir, Nadroparin, Bupropion, Fedratinib, Sargramostim, Fexinidazole, Netupitant, NSAIDS, Bemiparin, Aldesleukin	116,117,118

Table 5 - Systemic, Systemic, and Topical and Topical Corticosteroids use in OLP, PV, and MMP (106-144) (cont.)

International Common Name	Physicochemical Characteristics		Commercial name	Adverse Effects	Contraindications	Interactions	Bibliographic References
	Molecular Weight (mg/mol)	Chemical Formula	[Dosage | Pharmaceutical Form]				
Clobetasol Propionate	466.97	C25H32ClFO5	Clobetasol Cantabria [0.5 mg/g | Shampoo]; Clobetasol Cantabria [0.5 mg| Lotion]; Clobetasol Ratiopharm MG 0.5 mg/g [0.5 mg/g | Ointment]; Dermovate [0.5 mg/g | Lotion]; Dermovate [0.5 mg/g | Ointment]; Dermovate [0.5 mg/g | Cutaneous Solution]; Etrivex [0.5 mg/g | Shampoo];	Edema, Acne, Acneiform Eruption, Allergic contact dermatitis, Alopecia, Hyperpigmentation, Asteatotic eczema, Skin atrophy, Burning sensation, Dermatitis, Dry Skin, Erythema, Fissures in the skin, Folliculitis, Miliaria, Pruritus, Rash, Skin Irritation, Telangiectasia, Cushing's Syndrome, Delayed growth and development, Diabetes Mellitus, Hyperglycemia, Hypothalamic-pituitary-adrenal axis dysfunction,	Hypersensitivity to the corticosteroid or any other component of the product, Infection in the scalp	Auranofin, Bemiparin, Desmopressin, Glycerol Phenylbutyrate, Insulin Lispro, Macimorelin, Nadroparin, Sargramostim, Testosterone,	122,123,124
Fluticasona	444.51	C22H27F3O4S	Brisovent Diskus [100 or 250 or 50 µg/dose | Powder for Inhalation]; Brisovent Inalador 50 or 250 µg/dose | Powder for Inhalation]; Flixotaide Diskus [100 or 250 or 500 µg/dose | Powder for Inhalation]; Flixotaide Inalador [50 or 125 or 350 µg/dose | Pressurized solution for inhalation]; Flunutra [0.5 mg/g | Lotion]; Flutaide [50 µg/dose | Nasal Spray Suspension]; Fluticasona Nasofan [50 µg/dose | Nasal Spray Suspension]; Fluticrem [0.5 mg/g |Lotion]; Vibrocil Anti-Alergias [50 µg/dose | Spray Nasal Suspension];	Atrial fibrillation, Tachycardia, Vasculitis, Vasodilation, Impaired wound healing, Rash, Urticaria, Skin atrophy, Atopic dermatitis, Burning sensation, Dry Skin, Excoriation of skin, Pruritus, Stinging of skin, Adrenal Insufficiency, Cushing's syndrome, Decreased body growth, Hypercortisolism secondary to another disorder, Hyperglycemia, Type 2 Diabetes Mellitus, Candidiasis of mouth and esophagus, Nausea and Vomiting, Leukopenia, Thrombocytopenia, Increases liver enzymes, Backache, Osteoporosis, Headache, Glycosuria, Bleeding from the nose, Bronchitis, Cough, Nasopharyngitis, Pneumonia, Upper Respiratory Infection, Oral Candidiasis, Sinusitis,	Hypersensitivity to milk proteins, the corticosteroid or any component of the product, Status asthmaticus or other acute asthma episodes	Apalutamida, Auranofin, Bemiparin, Boceprevir and others of the same group, Bupropion, Ceritinib, Clarithromycin, Desmopressin, Fluconazole and other of the same group, Fosnepupitant, Glycerol Phenylbutyrate, Insulin Lispro, Nadroparin, Sargramostim, Testosterone	125,126,127

Table 5 - Systemic, Systemic, and Topical and Topical Corticosteroids use in OLP, PV, and MMP (106-144) (cont.)

International Common Name	Physicochemical Characteristics		Commercial name	Adverse Effects	Contraindications	Interactions	Bibliographic References
	Molecular Weight (mg/mol)	Chemical Formula	[Dosage | Pharmaceutical Form]				
Budesonide	430.5339	C25H34O6	Aeromax Nasal 100 µ [100 µg/dose | Suspension for Nasal Spray]; Budesonida Budinair [200 µg/dose | Pressurized Solution for inhalation]; Budesonida Farmoz [200 or 400 µg/dose | Powder for Inhalation] ; Budesonida Novolizer [200 or 400 µg/dose | Powder for Inhalation]; Budesonida Teva [1 mg/ 2 mL | Suspension for Inhalation by Nebulization]; Cetix Spray Nasal [64 µg/dose | Suspension for Nasal Spray]; Milfonide Breezhaler [200 or 400 µg/dose | Powder for Inhalation]; Pulmicort [1 mg/ 2 mL |Suspension for Inhalation by Nebulization]; Pulmicort Nasal Aqua [32 or 64 µg/dose | Suspension for Inhalation by Nebulization]; Pulmicort Turbohaler [200 or 400 µg/dose | Powder for Inhalation];	Hypertension, Peripheral edema, Dermatitis, Hirsutism, Diarrhea, Nausea, Arthralgia, Headache, Bleeding from nose, Dyspnea, Nasal stinging/burning, Respiratory tract infection, sinusitis, Edema of face, Fatigue. Syncope, Cushing's syndrome, Hyperglycemia, Hypercortisolism secondary to another disorder, Type 2 diabetes mellitus, Hypersensitivy reaction, Fracture of bone, Osteoporosis, Cataract, Glaucoma, Pneumonia, Angioedema	Hypersensitivity to budesonide or any components of the product, Milk proteins, Primary treatment of status asthmatics or other acute episodes of asthma requiring intensive intervention	Vaccines, Levoketoconazole, Desmopressin, Nirmatrelvir, Ritonavir, Fluoroquinolones, Ketoconazole, Conivaptan, Macimorelin, Lutetium Lu 177, Pacritinib, Nadroparin, Darunavir, Telaprevir, Ivosidenib, Bupropion, Fedratinib, Cyclosporine, Sargramostim, Lorlatinib, Lefamulin, Fexinidazole, Clarithromycin, Netupitant, Ceritinib, NSAIDS, Bemiparin	119,120,121

Table 5 - Systemic, Systemic, and Topical and Topical Corticosteroids use in OLP, PV, and MMP (106-144) (cont.)

International Common Name	Physicochemical Characteristics		Commercial name	Adverse Effects	Contraindications	Interactions	Bibliographic References
	Molecular Weight (mg/mol)	Chemical Formula	[Dosage | Pharmaceutical Form]				
Beclomethasone	521.042	C28H37ClO7	Beclotaide [50 µg/dose | Pressurized solution for inhalation]; Beclotaide Forte [250 µg/dose | Pressurized solution for inhalation]; Neo-Sinefrina Alergo [50 µg/dose | Nasal Spray Suspension]; Qvar Autohaler [100 µg/dose | Pressurized solution for inhalation];	Rosacea, Hypocortisolism secondary to another disorder, decreases body growth, Type 2 Diabetes Mellitus, Dental Pain, Nausea, Pharyngitis, Taste sense altered, Viral Gastroenteritis, Vomiting, Neutrophilia, Backache, Myalgia, Osteoporosis, Headache, Lightheadedness, Allergic rhinitis, Bleeding from the nose, Bronchospasm, Cough, Discomfort Nasal, Candidiasis, Nasopharyngitis, Sinusitis, upper respiratory Infection, Fever, Pain,	Hypersensitivity for beclomethasone or any ingredient of the product, Status asthmaticus or other acute asthma episodes	Bemiparin, Desmopressin, Glycerol Phenylbutyrate, Insulin Lispro Recombinant, Macimorelin, Nadroparin, Sargramostim, Testosterone	131,132,133
Fluocinolone Acetonide	452.4882	C24H30F2O6	Ekzem [0.1 mg/ 4 mL| Ear drops, Solution in single-dose container]; Synalar [0.25 mg/g | Lotion,];	Hypertension, Acneiform eruption, Skin Atrophy, Burning Sensation, Contact Dermatitis, Dry Skin, Erythema, Folliculitis, Hypertrichosis, Macerated Skin, Miliaria, Perioral Dermatitis, Pruritus, Rash, Secondary Infection, Skin Hypopigmentation and Irritation, Skin Striae, Telangiectasia Disorder, Hypercortisolism secondary to another disorder, Nausea, Vomiting, Anemia, Hypersensitivy Reaction, Influenza, Arthralgia, Backache, Pain in limb, Dizziness, Headache, Renal Failure, Cough, Nasal discharge. Nasopharyngitis, Pneumonia, Sinusitis, Upper Respiratory infection, Fever	Hypersensitivity to Fluocinolone or to any ingredients of the product; Glaucoma; With infections such as fungal diseases, mycobacterial infections, or viral diseases like herpes; vaccinia and varicella	Bemiparin, Desmopressin, Glycerol Phenylbutyrate, Insulin Lispro, Macimorelin, Nadroparin, Sargramostim, Testosterone	134,135,136

Table 5 - Systemic, Systemic, and Topical and Topical Corticosteroids use in OLP, PV, and MMP (106-144) (cont.)

International Common Name	Physicochemical Characteristics		Commercial name	Adverse Effects	Contraindications	Interactions	Bibliographic References
	Molecular Weight (mg/mol)	Chemical Formula	[Dosage | Pharmaceutical Form]				
Desonide	416.5073	C24H32O6	Zotinar [1 mg/g | Ointment]; Zotinar Capilar [1 mg/g | Cutaneous Solution];	Burning sensation, Cough, Upper respiratory system, Application site atrophy, Hypothalamic-pituitary-adrenal axis dysfunction, Raised intraocular pressure	Hypersensitivity to desonide or any component of the product		137,138,139
Mometasone	521.429	C27H30Cl2O6	Asmanex Twishthaler [200 or 400 µg/dose | Powder for Inhalation]; Desdek MG [1 mg/g | Lotion or Ointment]; Elocom [1 mg/g | Lotion or Ointment or Cutaneous Solution]; Mometasona Generis MG [50 µg/dose | Nasal Spray Suspension]; Mometasona Mylan [1 mg/g| Ointment]; Mometasona Ratiopharm [50 µg/dose | Nasal Spray Suspension]; Mometasona Sandoz [50 µg/dose | Nasal Spray Suspension]; Mometasona Teva [50 µg/dose | Nasal Spray Suspension]; Nasomet [50 µg/dose | Spray Nasal Suspension];	Infection by Candida albicans, Musculoskeletal pain, Headache, Dysmenorrhea, Bleeding from nose, Cough, Nasopharyngitis, Pharyngitis, Upper respiratory infection Allergic contact dermatitis, Adrenal insufficiency, Cushing's syndrome, decreased body growth, type 2 diabetes mellitus, Hypersensitivity reaction, Immunosuppression, Decreased bone mineral density, Cataract, Glaucoma, Raised intraocular pressure, Angioedema, Bronchospasm	Hypersensitivity to mometasone furoate or any other component, Milk proteins, Primary treatment of status asthmatics or other acute episodes of asthma requiring intensive intervention	Desmopressin, Nirmatrelvir, Ritonavir, Macimorelin, Lutetium Lu 177, Nadroparin, Sargramostim, Bemiparin	140,141,142

Table 5 - Systemic, Systemic, and Topical and Topical Corticosteroids use in OLP, PV, and MMP (106-144) (cont.)

International Common Name	**Physicochemical Characteristics**		**Commercial name**	**Adverse Effects**	**Contraindications**	**Interactions**	**Bibliographic References**
	Molecular Weight (mg/mol)	Chemical Formula	[Dosage | Pharmaceutical Form]				
Triamcinolone	394.4339	C21H27FO6	Bluxam [20 mg/mL| Injectable Suspension]; [200 or 400 µg/dose | Powder for Inhalation]; Nasacort [55 µg/Nasal Spray Suspension]; Telfast Spray Nasal 55 µg/dose | Nasal Spray Suspension];	Edema, Hypertension, Acne, Atrophy of the skin, Contact dermatitis, Ecchymosis, Burning sensation, Contusion, Erythema, Itching, Photosensitivity, Rash, Skin Irritation, Urticaria, Calcinosis, Cushing's syndrome, Decreased body growth, Hyperglycemia, Hyperthyroidism, Hypercortisolism secondary to another disorder, Hypokalemia, Lipids abnormal, Porphyria, Postmenopausal flushing, Gastrointestinal ulcer, Pancreatitis, Diarrhea, Indigestion, Oral candidiasis, Tooth disorder, Vomiting, Xerostomia, Hepatomegaly, Osteoporosis, Backache, Myalgia, Headache, Candidiasis, Cough, Bleeding from nose, Nasopharyngitis, Pulmonary congestion, Sinusitis	Hypersensitivity to triamcinolone or any ingredient of the product, Concomitant infections (viral, fungal, mycobacterial, and viral such herpes, vaccinia, and varicella), Concomitant administrate of live or live attenuated vaccines, Idiopathic Thrombocytopenic purpura, Status asthmaticus or acute asthma,	Vaccines, Aspirin, Ciprofloxacin and other antibiotics of the same class, Desmopressin, Glycerol Phenylbutyrate. Macimorelin, Nadroparin, Phenobarbital, Testosterone, Warfarin, Sargramostim	128,129,130

Table 5 - Systemic, Systemic, and Topical and Topical Corticosteroids use in OLP, PV, and MMP (106-144) (cont.)

International Common Name	Physicochemical Characteristics		Commercial name	Adverse Effects	Contraindications	Interactions	Bibliographic References
	Molecular Weight (mg/mol)	Chemical Formula	[Dosage | Pharmaceutical Form]				
Betamethasone	392.4611	C22H29FO5	Betametasona Basi [1 mg/g | Lotion]; Betametasona Cantabria [1 mg/g | Cutaneous Solution]; Betnovate [1 mg/g | Lotion]; Betnovate Capilar [Cutaneous Solution| Tablet]; Celestone [0.5 mg/mL | Oral Solution]; Cilestoderme [1 mg/g | Lotiont]; Diprofos Depot [14 mg/ 2 mL |Injectable Suspension]; Diprosone [0.5 mg/g | Lotion; Ointment]; Diprosone N.V. [0.5 mg/g | Ointment]; Soluderme [0.5 mg/g | Cutaneous Solution];	Hypertension, Acne, Acneiform eruption, Alopecia, Skin atrophy, Burning sensation, Contact dermatitis, Dry skin, Ecchymosis, Folliculitis, Miliaria, Onychomycosis, Pruritus of skin, Stinging of skin, Vesicle of skin, Cushing's syndrome, Weight gain, Growth retardation, Hyperglycemia, Hypercortisolism secondary to another disorder, Lipids abnormal, Hypothalamic. Pituitary-adrenal- axis dysfunction, Gastrointestinal ulcer, Oropharyngeal candidiasis, Osteoporosis, Glycosuria, Pulmonary tuberculosis,	Hypersensitivity to the corticosteroid or any other component of the product,	Aceclofenac and others of the same group, Acemetacin, Vaccines, Aspirin, Bemiparin, Bupropion, Carbamazepine, Celecoxib and others of the same group, Ciprofloxacin and other antibiotics of the same class, Desmopressin, Desogestrel and other contraceptives, Echinacea, Insulin Lispro, Ibuprofen, Indomethacin, Meloxicam, Nadroparin, Phenobarbital, Rifampicin, Ritonavir, and others of the same group, Sargramostim, Testosterone	113,114,115

6. Therapeutic Algorithm

Although the treatment differs between the three pathologies, there are some non-pharmaceutical therapeutics that can be done in all three like avert spicy, acid, or salty foods, maintaining the teeth clean with the use of a soft brush and an interdental brush, picking a toothpaste that has a mild flavor and without the excipient sodium lauryl sulfate, consulting regularly a dentist or an oral specialist to bypass the reduce the risk of development of cancer and to decrease the smoking and the alcohol intake to 14 units weekly for both genders. (21,25).

6.1. Oral Lichen Planus

As shown in Figure 9, the OLP course of the treatment depends on several factors (36,145).

If the OLP is erosive or has the presence of symptoms, it is necessary to add topical corticosteroids with a low or mild potency seen in table 3 (36,145). If required, according to the patient's characteristics could be vital to switch to intralesional corticosteroids (36,145).

After the duration of the treatment mentioned above, if there are no improvements, it is vital to switch to a topical corticosteroid of higher potency and add an antifungal (36,145).

After three weeks of treatment, if there is a halfway resolution, there is a demand to continue the previous treatment for a limit of 6 months (36,145).

If there is no resolution, it is necessary to apprehend if there is or is not a medical reason to add systemic corticosteroids (36,145).If not, then is added. If there is, then immunosuppressive agents are the answer (topical Tacrolimus or Pimecrolimus) (36,145).

Nevertheless, if it is unsolved, it is necessary to go with unconventional therapies like retinoids, PUVA, and iodine laser (36,145).

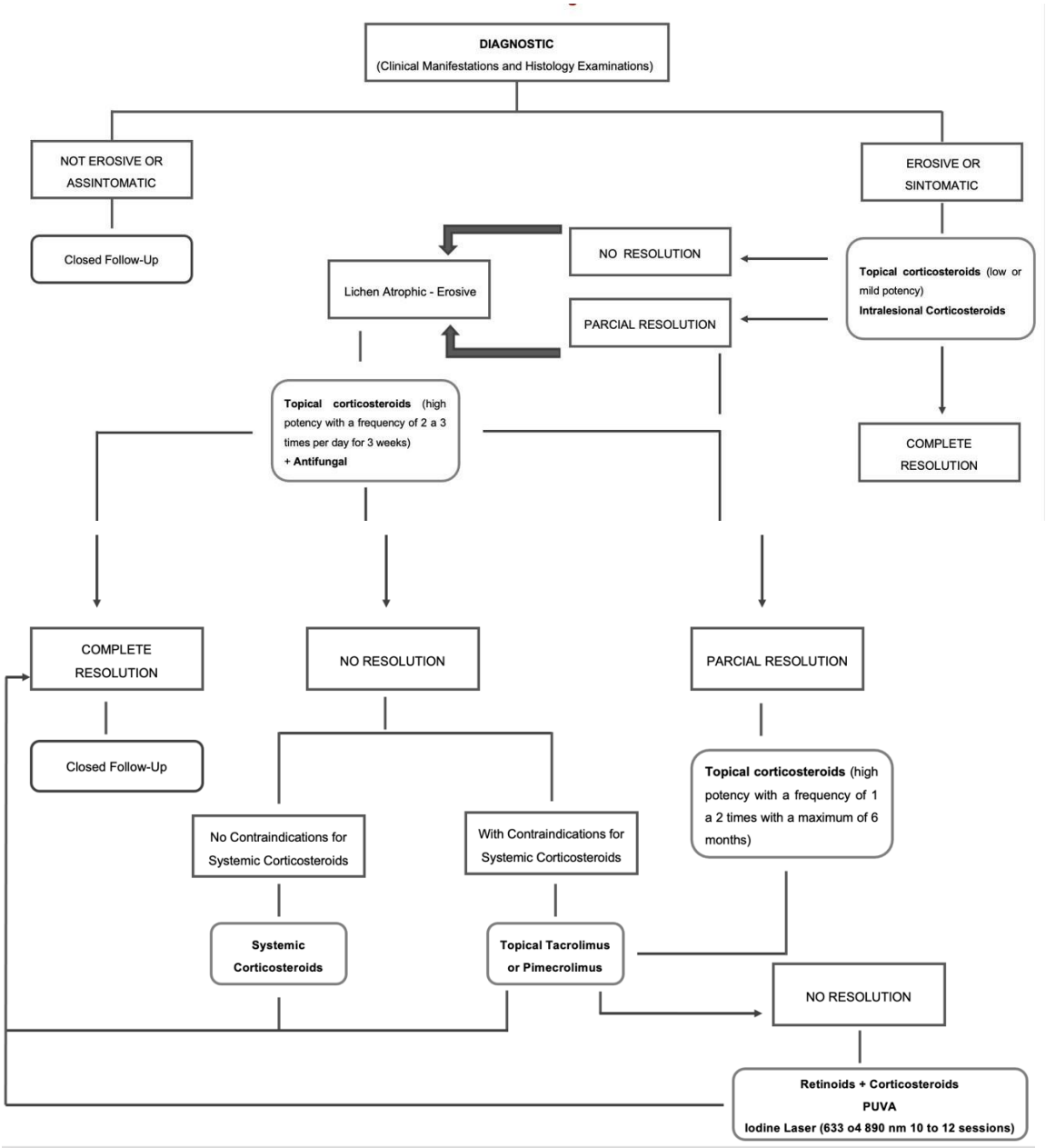


Figure 9 - Therapeutic Algorithm of Oral Lichen Planus (36,145)

6.2. Pemphigus Vulgaris

As perceived in Figure 10, the course of treatment depends on the percentage of the superficies involved (146,147).

If there is little than five % of the superficial corporal area affected, there is a need for systemic corticosteroids or Rituximab. If needed, it could be added topical corticosteroids (146,147).If there is a midway resolution, it is necessary to conjoin other therapies (Azathioprine, Mycophenolate mofetil, or Mycophenolate sodium) (146,147).

Nevertheless, if there is a halfway resolution, it is necessary to increase and change the systemic corticosteroid and conjugate the systemic corticosteroids and the Rituximab (146,147). If there is still a mid-resolution, there is a necessity for other therapies specifically IV immunoglobulins or plasmapheresis (146,147).

When there is a complete resolution, it is needed to diminish the dose of the systemic corticosteroids and sustain the treatment for three months (146,147).

If there is more than five % of the superficial corporal area of the oral mucosa affected and other mucosa involved, the treatment could be systemic corticosteroids, Rituximab, and the association between the systemic corticosteroids and Rituximab (146,147).

After three to four months of treatment, if there is no or mid-way resolution is necessary for the treatment to be Rituximab and the systemic corticosteroid, with an uprise of the levels of the systemic corticosteroid (146,147).If demand, other therapies could be added like azathioprine (146,147).

When there is a full resolution, it is essential to prolong the treatment for 18 months, depending on the levels of antibodies (146,147).

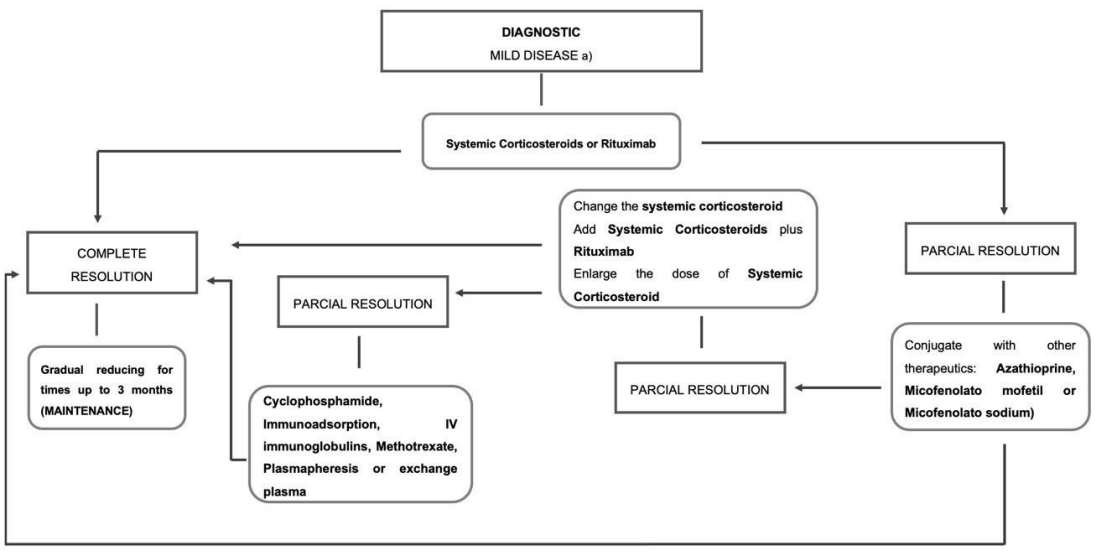
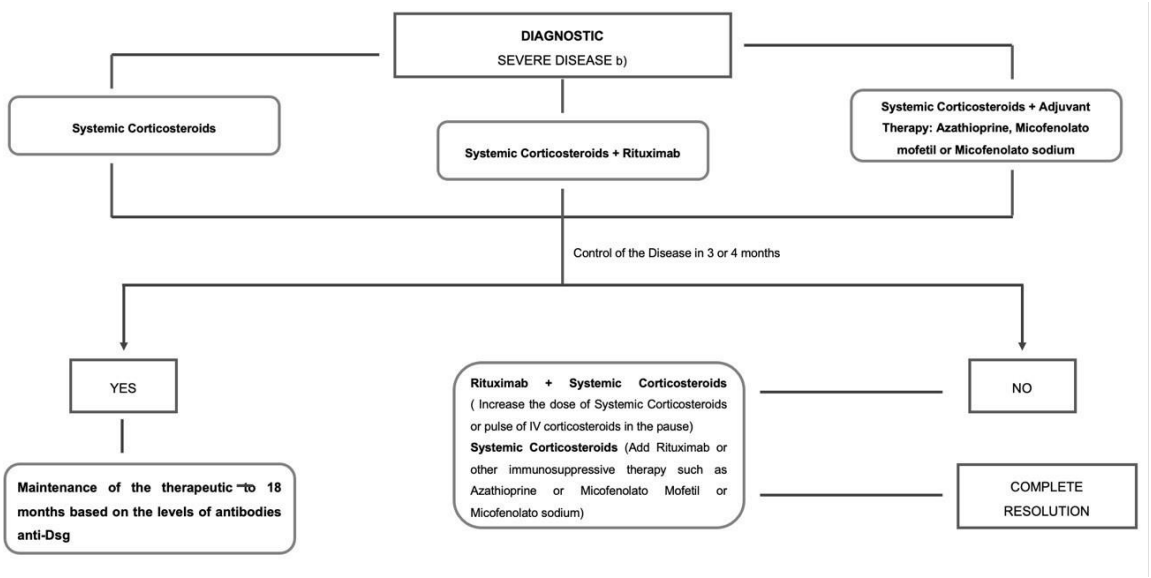


Figure 10 – Therapeutic Algorithm of Pemphigus Vulgaris (146,147)



a) Involvement of other superficies with less than 5% of the superficial corporal area and or the oral mucosa that does not withhold the ingestion of food or requires painkillers and or PDAI score inferior of 15
b) Involvement of multiple mucous such as oral, nasopharyngeal, conjunctival, and genital mucosae, with several lesions on the oral mucosa and or skin lesions superior to 5% of the superficial corporal area with a PDAI score above 45

Figure 10 - Therapeutic Algorithm of Pemphigus Vulgaris (146,147) (cont.)

6.3. Mucous Membrane Pemphigoid

The MMP therapeutics depends on the risk for the patient as shown in Figure 11 (83,148,149).

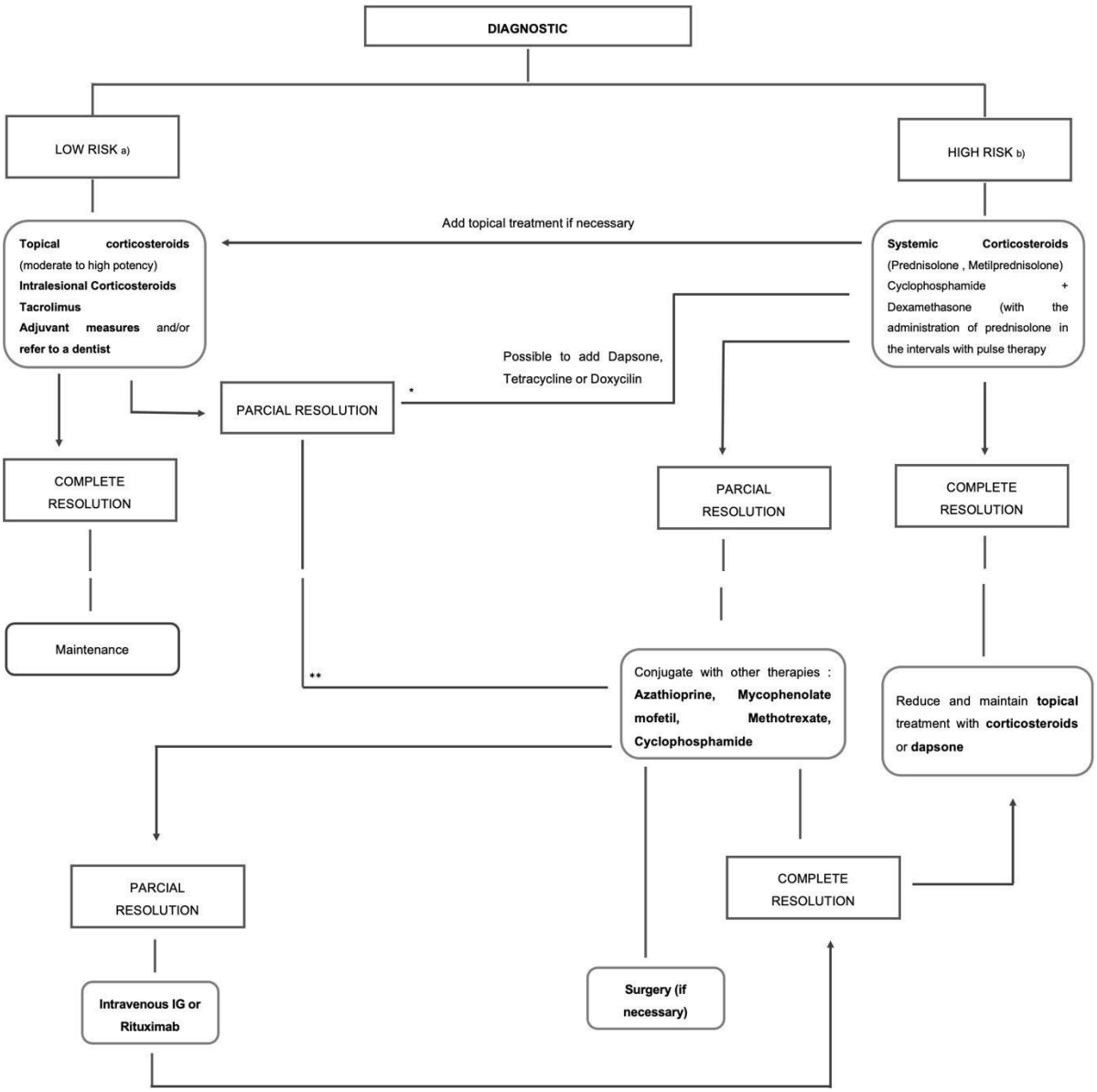
If this disease only develops in the oral mucosa, the initial course of treatment is the addition of topical corticosteroids of moderate to high potency, as seen in table 3 (83,148,149). Other alternative therapies may be a possibility like intralesional corticosteroids or tacrolimus (83,148,149).

If there is a halfway resolution, the course of treatment is the same as if the disease involves the oral, ocular, genital, esophagus, or larynx mucosae (83,148,149).

If this disease is widespread in the oral mucosa or if involves other mucosae, the course of therapy consists of systemic corticosteroids, and there is a possibility that topical treatment could be necessary (83,148,149).

If there is a partial or no resolution it is necessary to associate the systemic corticosteroids, with other medicines like azathioprine, mycophenolate mofetil, methotrexate, or cyclophosphamide (83,148,149).

After the duration of treatment, if there is a halfway resolution, the treatment could be IG or Rituximab. If there are not any improvements, surgery may be indispensable. When there is a resolution, the course of treatment is to diminish and maintain the systemic corticosteroids (83,148,149).



a) Involves the mucosa oral with or without the implication of the skin, without the involvement of the ocular, genital, esophagus, or larynx mucosae

b) Diffuse or a progression in the oral mucosa, with the involvement of ocular, genital, esophagus, or larynx mucosae

Figure 11 - Therapeutic Algorithm of Mucous Membrane Pemphigoid (83,148,149).

7. Trends in Corticosteroids in Pharmaceutical Formulations

Nowadays, there is a deficiency in the variety of topical pharmaceutical forms accessible in the market to use in the oral manifestations of autoimmune mucocutaneous diseases (31). There are some impediments when talking about buccal delivery such as the existence of saliva and its constant turnover, taste, the restricted surface area, faulty tissue penetration, enzyme degradation, and unintended swallowing (31). Also, long, or potent contact corticosteroids show atrophic repercussions in the oral mucosa.

The present available pharmaceutical forms have a lot of drawbacks such as:

- The existing pharmaceutical forms of corticosteroids in the market are more adequate for exterior dermatologic issues than oral tissues (150);
- The excipients used in the commercial pharmacies available are not the most adequate to use in the oral cavity like the ones that aggravate symptoms (flavor, color, or alcohol) and therefore should not be used (151- 154).

One of the pharmaceutical forms most used that results in a better prognosis for the person is mouth rinses (31). However, there are no oral rinses available or the ones that are commercialized have excipients like isopropyl alcohol, flavoring, and acid buffers that could potentially worsen this type of disease (31).

At the present, what is done in clinical practice is to macerate tablets of dexamethasone (0.5 mg) and blend them with water (155) Although, there is amelioration in the conditions there are a lot of disadvantages like some excipients in the tablets resulting in a grainy and distasteful formulation, adversity in the preparation of this pharmaceutical forms, which could lead to undetermined therapeutic dosage, and a faulty adherence (155).

As seen in the chapters before, there are currently a lot of pharmaceutical forms available like ointments, pastes, lozenges, mouthwashes, sprays, adhesive pastes, rinses, tablets, suspensions, creams, gels, chewing gums, and lollipops (156-159). However, these pharmaceutical forms not only bring a lot of disadvantages to the patient like a constant application throughout the day but also other characteristics like the presence of

saliva or a not homogenous layout of the medicine in the whole cavity, for example, that compromises the prognostic of this disease (160).

Thereby, to bypass all these factors there is a need to investigate and commercialized other pharmaceutical forms that are more suitable to achieve an optimal buccal delivery. Therefore, the new pharmaceutical forms that are in their early steps not only with corticosteroids but also with other groups of active substances are as illustrated in Figure 12:

- Hydrogels

Hydrogels or "wet adhesives" consist of a 3D hydrophilic, polymeric net that has the capacity of absorbing sizeable amounts of water (161). They consist of hydrophilic polymeric matrices that swell in the presence of an aqueous environment like saliva (162). Their mechanism of action consists of an infinitely swelling, where the components of the medicine diffuse from the surface of the matrix (163). They are constituted by cross-linked swollen polymers having water ranging from 30 to 40 %. There is a variety of polymers that can be used like polyacrylates, ethylene vinyl alcohol, polyethylene oxide, polyvinyl alcohol, polyoxyethylene, self-cross linked with gelatin, sodium alginate, and natural gums (164). Therefore, they are particularly helpful in the adherence of the mucosa and enlarge the amount of time that this pharmaceutical form remains in the buccal cavity (165). Nowadays, the hydrogels are being blended with other pharmaceutical forms resulting in micro or nano gels, as an example is being formulated the antifungal miconazole in a nanostructured lipid carrier (166). At this moment, there are none of the corticosteroid hydrogels being studied, only have been investigating systemic analgesics, anti-hypertensive, anti-inflammatories, antifungal, and mucoprotective agents (167 -171).

- Buccal films or patches

Buccal films or patches consist of a type of drug formulation that has a different route of administration through the buccal mucosa for drug delivery, with a likelihood of directly entering the blood mainstream bypassing the hepatic first-pass metabolism (172). There are a lot of advantages when compared with buccal adhesive tablets like the

flexibility, comfort, protection of wound surfaces, reduce the pain and enlarge the effectiveness of the treatment (162). Also, they have the advantage over creams and ointments due to allowing an accurate measure of the dosage of the drug (173) There are a variety of buccal films like matrix-controlled, membrane-controlled, and biodegradable or erodible formulations (174). They are constituted by the active ingredient selected based on pharmacokinetic properties, polymers which may vary from mucoadhesive polymers (Cellulose derivatives, Natural gums, Starch, Sodium alginate, Polyvinyl pyrrolidone, Polyethylene oxide, Polyethylene glycol), polymers controlling the rate of release (Ethyl cellulose and Butyl rubber), a backing membrane with a function to provide a unidirectional medicament movement to the buccal mucosa (Polyester laminated paper with Polyethylene, Cellophane-325, Multiphor sheet, Polyglassine paper), plasticizer to give the softness and the flexibility to the films (Glycerol, Propylene glycol, Polyethylene glycol 200, Polyethylene glycol 400, and castor oil) and the penetration enhancers that increase the chances of drug permeation (surfactants, anions, cations, nonions, fatty acids, cyclodextrins, and protease inhibitors) (162,174-176). Now, Chun et al, are investigating buccal mucoadhesive patcheswith the active ingredient of triamcinolone acetonide with the polymers Carbopol, poloxamer, and Hydroxypropyl Methylcellulose (162). This form of pharmaceutical form is already being used in the treatment of migraines with a rapid and efficacious treatment (177).

- Buccal Adhesive Tablets

The buccal adhesive tables are not constituted by a disintegrant agent (162). Consequently, they have the tendency to endure longer in the oral cavity (178). They consist of an incorporated drug polymeric matrix with a backing impermeable membrane, with a rate of release managed by diffusion (178). The ideal buccal adhesive drug delivery system must contain the mucoadhesive polymer with the function of continuing and lengthening the contact between the formulation and the site of absorption (Polyacrylic acid, Polyvinyl alcohol, sodium carboxymethylcellulose, Hydroxypropyl methylcellulose, Hydroxyethylcellulose, Hydroxypropyl cellulose, Sodium alginate, Chitosan, Gelatin, Carrageenan, Lamellar, Glyceryl monooleate), the penetration enhancers with a function to improve penetration of the drug in the mucosa or in the epithelium (thiolated polymers, Surfactants, Chelators, Non-surfactants, Fatty

acids, Inclusion complexes, Bile salts) and the enzyme inhibitors that shield the drug against the degradation of the mucosal enzymes (Aprotinin, Bestatin, Puromycin, Bile salts) (173,179- 183). There are two types of buccal adhesive tablets like the mono-layered tablets where there is a mix between the drug and the mucoadhesive polymer, resulting in a bidirectional release, and a double-layered tablet which consists of an internal layer constituted of the bioadhesive polymer and external layer with a non-bioadhesive containing the drug with a bidirectional local action release (184-187). Now, there are four corticosteroid buccal adhesive tablets formulations triamcilone with the polymers of Hydroxypropyl Cellulose, Carbopol-934 or Hydroxypropyl methylcellulose and PADH, the hydrocortisone acetate with Hydroxypropyl methylcellulose, Carbopol-934P, Polycarbophil, and the prednisolone with polycarbophil and Carbopol-934P (188-191).

- Microparticles

The bioadhesive particles have the same advantage as the tablets (173). However, their properties allow them to make close contact with the biggest mucosal surface area. Also, they have the capacity of reaching less approachable sites like the gastrointestinal tract and the upper nasal cavity (192). In addition, when we balance the size between the microparticles and the tables they are minor, with a consequence of a lessing of the adverse effects (local irritation and the unbearable sensation of a strange object (192). Studies have been made with the use of microparticles for the treatment of dental caries, which determined that microparticles constituted by the bioadhesive polymer, the chitosan, the cross-linked agent, glutaraldehyde, and the active substance, fluoride demonstrate a better outcome with a small concentration of chitosan, with an initial high-speed release continuing with a lengthy slow-moving release resulting in a period of release of 6 hours (193). These microparticles were made using a spray-drying, with a control quality in terms of particles size, the capability of encapsulation ,and the release of the medicament (161).

- Liposomes

The liposomes consist of little artificial vesicles with a spherical shape that can be made of cholesterol and natural phospholipids (194). Using the liposomes as a method of drug delivery helps to enlarge the retention of the drug in the oral cavity, demining

the systemic effects and the dissemination to other adjacent tissues (195), for example, liposomes of triamcinolone acetonide lead to a bigger dosage in the oral mucosa when compared to the control (195). They are some disadvantages like the difficulty to control the profile release and the restricted ability to improve the characteristics since they are naturally made of proteoglycans (196). On the other side, it compensates with a lot of advantages such as an accumulation in the higher layer of the epidermis due to a resemblance which results in a shield against the metabolic degradation, a rise in the half-life of the drugs, the topical efficiency, a diminishing of the side effects, control of the dosage, the release of the drug, the capacity to accumulate the medicament, biocompatibility, biodegradability, a rise in the local concentration and a decline in the systemic drug concentration (197,198). At this moment, the liposomes are being studied as a drug delivery carrier in pastes and solutions (184,199), namely, a liposome encapsulating corticosteroids in a paste may induce the absence of symptoms in the treatment of OLP (200), resulting in a triamcinolone acetonide 0,1 % nano liposomal being more effective, with a decrease of the pain and size of the lesions of OLP that the 0.1% triamcinolone paste (Orabase) (201).

Figure 12 New Perspectives of Pharmaceutical Forms for Treatment of OLP, PV, and MMP (A – Hydrogels, B – Multilayered Tablets, C – Films or Patches, D – Buccal Adhesive Tablets, E- Mechanism of Action of Microparticles, F – Structure of Liposomes) (202-207)

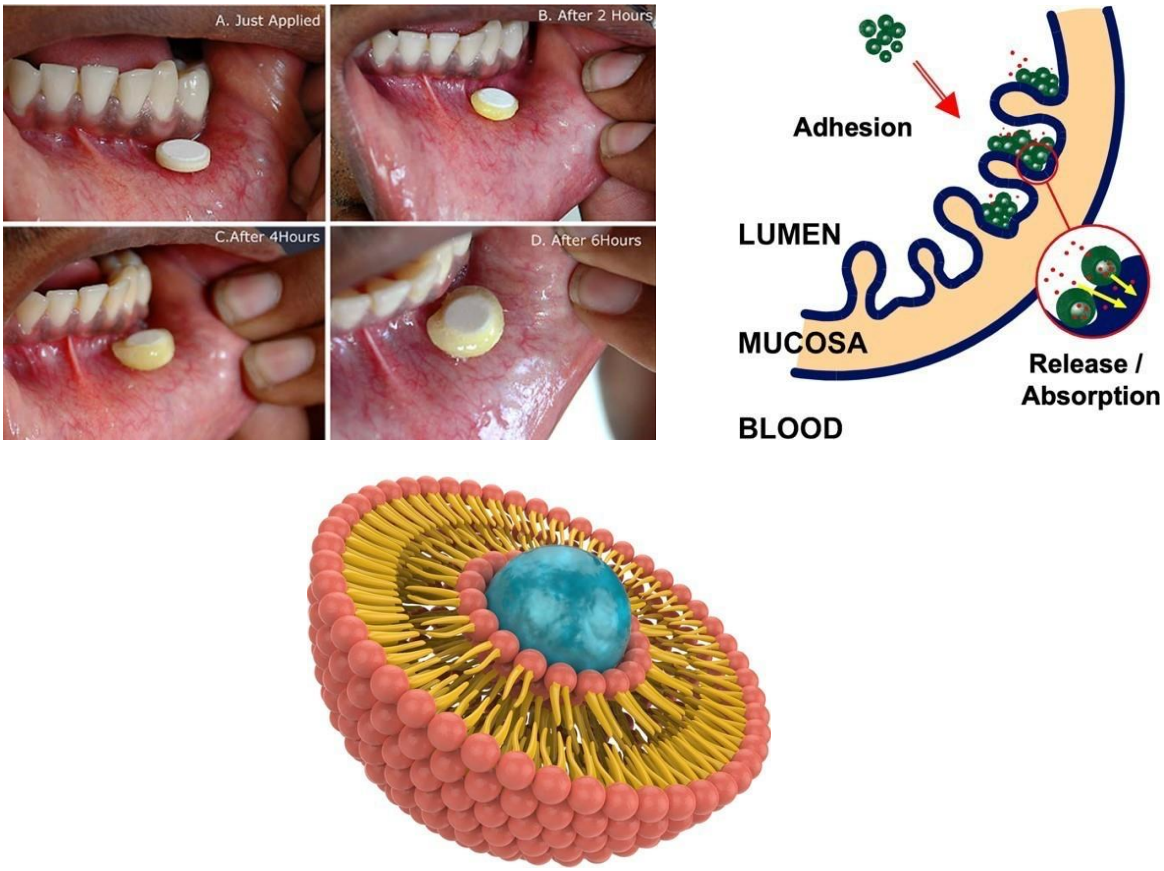


Figure 12 - New Perspectives of Pharmaceutical Forms for Treatment of OLP, PV, and MMP (A – Hydrogels, B – Multilayered Tablets, C – Films or Patches, D – Buccal Adhesive Tablets,E- Mechanism of Action of Microparticles, F – Structure of Liposomes) (202-207) (cont.)

8. Conclusions

The oral cavity corresponds to a mirroring of a person's health. This can be affected by various microorganisms, but it is the autoimmune diseases of the oral mucosa that enhances the chances of increased mortality and morbidity.

Various autoimmune diseases can affect the mucous membrane. However, the most prevalent consist of the Oral Lichen Planus, Pemphigus Vulgaris, and Mucous Membrane Pemphigoid.

OLP does not have a mechanism of action fully known. However, from what is known, it presents an autoimmune inflammatory mechanism mediated by CD8+ cells, macrophages, and Langerhans cells, activated by various factors. PV has the capacity of causing intra-epithelial blistering since the IG autoantibodies directly attack the desmosomes. The MMP leads to sub-epithelial blistering because the IG autoantibodies are against the hemidesmosomes localized in the basal membrane zone.

For all three pathologies, corticosteroids correspond to the first choice of medicines. When treating the OLP, the most used are the topical corticosteroids, and the systemic corticosteroids are reserved for more severe cases. For the remaining pathologies, the ones that are most utilized are the systemic corticosteroids, but topical corticosteroids can be used as a coadjutant treatment.

The corticosteroids have anti-inflammatory, anti-proliferative, and vasoconstrictor activity, diversifying from low potency to ultrahigh potency. They can lead to adverse effects, local or systemic, especially if they are used in high dosages or if they are utilized for prolonged periods.

However, the pharmaceutical forms available in Portugal are insufficient for the treatment of cavity oral diseases due to various factors like the presence of saliva, mechanical stress, and use of certain excipients, but also to the demands of the patient, concerning the adherence. At this moment, several pharmaceutical forms are being investigated, in a way to be more adequate for pathologies inside the oral cavity. However, there is a need to take a step forward and advance to phase III and IV clinical trials and to eventually commercialized new pharmaceutical forms, not only to exist new

forms of treatment more suitable to the oral cavity but also to lessen the mortality, morbidity, and prognostic associated with these pathologies.

9. Bibliography

1. Sciubba JJ. Autoimmune Oral Mucosal Diseases: Clinical, Etiologic, Diagnostic, and Treatment Considerations. Dental Clinics of North America. 2011 Jan; 55(1): 89–103. PubMed; PMID: 21094720.
2. Mark R. Blistering Mucocutaneous Diseases of the Oral Mucosa — A Review: Part 1. Mucous Membrane Pemphigoid. J Can Dent Assoc. 2005 Dec; 71 (11): 851- 4. PubMed. PMID: 1648600.
3. Schmidt E, Zillikens D. Pemphigoid diseases. Lancet. 2013 Jan;381(9863): 320–32. PubMed. PMID:23237497.
4. Mustafa MB, Porter SR, Smoller BR, Sitaru C. Oral mucosal manifestations of autoimmune skin diseases. Autoimmunity Reviews. Elsevier. 2015 Oct;14 (10): 930–51.PubMed. PMID:26117595.
5. Krupaa RJ, Sankari SL, Masthan KMK, Rajesh E. Oral lichen planus: An overview. Journal of Pharmacy and Bioallied Sciences. Wolters Kluwer Medknow Publications. 2015 Apr; 7 (Suppl 1): 158–61. PubMed. PMID: 26015968.
6. Alrashdan MS, Cirillo N, McCullough M. Oral lichen planus: a literature reviewand update. Archives of Dermatological Research. Springer Verl. 2016 Oct; 308 (8); 539-51. PubMed. PMID:27349424.
7. Kurago ZB. Etiology and pathogenesis of oral lichen planus: An overview. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. Mosby Inc. 2016 Jul; 122 (1): 72–80. PubMed. PMID: 27260276.
8. Hasan S, Ahmed S, Kiram R, Panigraphi R, Thacil J, Saeed S. Oral lichen planus and associated comorbidities: An approach to holistic health. J Fam Med Prim Care. 2019 Nov; 8 (11); 3504-3517. PubMed. PMID:31803644.
9. Eisen D, Carrozzo M, Sebastian J-VB, Thongprasom K. Oral lichen planus: clinical features and management. Number V. Oral Dis. 2005; 11(6): 338-349.
10. Popescu I, Statescu L, Vata D, Andrese E, Patrascu A, Grajdeanu I-A, et al. Pemphigus vulgaris - approach and management (Review). Exp Ther Med. 2019Dec; 18(6): 5056-5060. PubMed. PMID: 31819769.
11. Buonavoglia A, Leone P, Dammacco R, Di Lernia G, Petruzzi M, Bonamonte D, et al. Pemphigus and mucous membrane pemphigoid: An update from diagnosis to therapy. Autoimmunity Reviews. Elsevier B.V. 2019 Apr; 18(4):349–358. PubMed. PMID: 30738958.

12. Costan V-V, Popa C, Hâncu M, Porumb-Andrese E, Toader M. Comprehensive review on the pathophysiology, clinical variants and management of pemphigus(Review). Exp Ther Med. 2021 Sep 20; 22(5): 1335. PubMed. PMID: 34630689.
13. Schmidt E, Kasperkiewicz M, Joly P . Pemphigus. Lancet. 2019 Sep; 394 (10201): 882-894. PubMed. PMID: 31498102.
14. Malik AM, Tupchong S. Huang S, Are A, Hsu S, Motaparthi K, An updated reviewof pemphigus diseases. Medicina (Lithuania). MDPI. 2021 Oct.57(10): 1080. PubMed. PMID: 34684117.
15. Rashid H, Lamberts A, Diercks GFH, Pas HH, Meijer JM, Bolling MC, et al. Oral Lesions in Autoimmune Bullous Diseases: An Overview of Clinical Characteristics and Diagnostic Algorithm. American Journal of Clinical Dermatology. Adis. 2019 Dec; 20(6): 847– 61. PubMed. PMID: 31313078.
16. Carey B, Setterfield J. Mucous membrane pemphigoid and oral blistering diseases. Clinical and Experimental Dermatology. Blackwell Publishing Ltd. 2019 May; 44(7): 732–9. Wiley Online Library. doi: **10.1111/ced.13996**
17. Kridin K. Subepidermal autoimmune bullous diseases: overview, epidemiology,and associations. Immunologic Research. Humana Press Inc. 2018 Feb; 66(1): 6-17.PubMed. PMID: 29159697.
18. Carrozzo M, Porter S, Mercadante V, Fedele S. Oral lichen planus: A disease or a spectrum of tissue reactions? Types, causes, diagnostic algorhythms, prognosis, management strategies. Periodontology 2000. Blackwell Munksgaard. 2019 Jun;80(1); 105–25. PubMed. PMID: 31090143.
19. Mutafchieva MZ, Draganova-Filipova MN, Zagorchev PI, Tomov GT. Oral lichen planus – known and unknown: a review. Folia Medica (Medline). 2018 Dec; 60(4): 528-35. PubMed. PMID: 3188760.
20. Jascholt I, Lai O, Zillikens D, Kasperkiewicz M. Periodontitis in oral pemphigus and pemphigoid: A systematic review of published studies. Journal of the American Academy of Dermatology. Mosby Inc.2017 May; 76(5): 975-978.e3. PubMed. PMID: 28038889.
21. British Association of Dermatologists [Internet]. Bad.org.uk. 2022 [cited 15 April 2022]. Available from: https://www.bad.org.uk/pils/oral-lichen-planus/
22. Neff AG, Turner M, Mutasim DF. Treatment strategies in mucous membrane pemphigoid. Ther Clin Risk Manag. 2008 Jun;4(3):617–26. PubMed. PMID: 18827857.

23. Knudson RM, Kallaj AN, Bruce AJ. The management of mucous membrane pemphigoid and pemphigus. Dermatol Ther. 2010 Jun;23 (3):268-80. PubMed. PMID: 20597945.
24. Gonzalez-Moles MA, Ruiz-Avila I, Rodriguez-Archilla A Morales-Garcia P, MesaAguado F, Bascones-Martinez A, et al. Treatment of severe erosive gingival lesions by topical application of clobetasol propionate in custom trays. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003 Jun;95(6):688-92.PubMed. PMID: 1278149.
25. British Association of Dermatologists [Internet]. Bad.org.uk. 2022 [cited 15 April 2022]. Available from: https://www.bad.org.uk/pils/mucous-membrane- pemphigoid/
26. British Association of Dermatologists [Internet]. Bad.org.uk. 2022 [cited 15 April 2022]. Available from: https://www.bad.org.uk/pils/pemphigus-vulgaris/
27. Cooney WP. Compound F: The History of Hydrocortisone and Hand Surgery. J Hand Surg Am. 2013 Apr 1;38(4):774–8. PubMed. PMID: 23403170.
28. Bandyopadhyay D. A treatise on topical corticosteroids in dermatology. Use, misuse and abuse. Indian J Dermatol Venereology Leprology. 2018;84(6):761-762.Indian Journal of Dermatology, Venereology and Leprology. PMID:30264746.
29. Mehta A, Nadkarni NJ, Patil SP, Godse K V., Gautam M, Agarwal S. Topical corticosteroids in dermatology. Indian Journal of Dermatology, Venereology and Leprology. Medknow Publications.2016 Jul-Aug; 83(4):371-8. PubMed. PMID: 27279294.
30. Corticosteroids [Internet]. Nhsinform.scot. 2022 [cited 22 March 2022]. Available from: https://www.nhsinform.scot/tests-and-treatments/medicines-and-medical-aids/types-of-medicine/corticosteroids
31. Hambly JL, Haywood A, Hattingh L, Nair RG. Comparison between self- formulation and compounded-formulation dexamethasone mouth rinse for oral lichen planus: a pilot, randomized, cross-over trial. J Investig Clin Dent. 2017 Aug;8(3):e12225. PubMed. PMID: 27344987.
32. Saúde-Infopédia Dicionários [Internet]. Infopédia – Porto Editora. 2022 [cited 15 March 2022]. Available from: https://www.infopedia.pt/apoio/artigos/$saude
33. Dicionário Priberam. Doença [cited 15 March 2022]. [Internet]. Available from: https://dicionario.priberam.org/doen%C3%A7a%20%5BInternet%5D%20%5Bcited%2015%20March%202022%5D.

34. Leuci S, Ruoppo E, Adamo D, Calabria E, Mignogna MD. Oral autoimmune vesiculobullous diseases: Classification, clinical presentations, molecular mechanisms, diagnostic algorithms, and management. Periodontology 2000. 2019 Jun; 80(1):77–88. PubMed. PMID: 31090146.
35. Lodi G, Pellicano R, Carrozzo M. Hepatitis C virus infection and lichen planus: a systematic review with meta-analysis. Oral Dis. 2010 Oct; 16(7): 601-12. PubMed. PMID:20412447.
36. Lavanya N, Jayanthi P, Rao U, Ranganathan K. Oral lichen planus: An update on pathogenesis and treatment. Journal of Oral and Maxillofacial Pathology. 2011 May; 15 (2): 127–32. PubMed: 22529568.
37. Łukaszewska-Kuska M, Ślebioda Z, Dorocka-Bobkowska B. The effectiveness of topical forms of dexamethasone in the treatment of oral lichen planus— A systematic review. Oral Diseases. John Wiley and Sons Inc; 2021 Jul. PubMed. PMID: 34273228.
38. Ismail SB, Kumar SK, Zain RB. Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis, management and malignant transformation. J Oral Science. 2007 Jun; 49(2):89-106. PubMed. PMID: 17634721.
39. Bermejo A, Aguirre JM, López P, Saez MR. Superficial mucocele: report of 4 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999 Oct; 88(4):469-72. PubMed. PMID: 10519757.
40. Eveson JW. Superficial mucoceles: pitfall in clinical and microscopic diagnosis. Oral Surg Oral Med Oral Pathol. 1988 Sep; 66(3): 318-22. PubMed. PMID: 3174068.
41. Hawk JLM. Lichenoid drug eruption induced by propanolol. Clin Exp Dermatol. 1980 Mar; 5(1):93-6. PubMed. PMID: 7398132.
42. Hamburger J, Potts AJ. Non-steroidal anti-inflammatory drugs and oral lichenoid reactions. Br Med J (Clin Res Ed). 1983 Oct; 287(6401): 1258. PubMed. PMID: 6416356.
43. Cutler TP. Lichen planus caused by pyrimethamine. Clinical andExperimental Dermatology. 1980 Jun; 5 (2): 253-6. PubMed. PMID: 6449324.
44. Lamey P, Gibson J, Barclay SC, Miller S. Grinspan's syndrome: a drug-induced phenomenon? Oral Surg Oral Med Oral Pathol. 1990 Aug; 70(2); 184-5. PubMed. PMID: 2290647.
45. Walton KE, Bowers EV, Drolet BA, Holland KE. Childhood lichen planus: demographics of a U.S. population. Pediatr Dermatol. 2010 Jan-Feb;27(1):34-8. PubMed. PMID: 20199407.

46. Eisen D. The clinical manifestations and treatment of oral lichen planus. Dermatol Clin. 2003 Jan; 21(1): 79-89. PubMed. PMID: 12622270.
47. Mustafa MB, Porter SR, Smoller BR, Sitaru C. Oral mucosal manifestations of autoimmune skin diseases. Autoimmunity Reviews. 2015 Oct;14(10):930-51. PubMed. PMID: 26117595.
48. Kridin K. Pemphigus group: overview, epidemiology, mortality, and comorbidities. Immunologic Research. Humana Press Inc.; 2018 Apr; 66(2): 225-270. PubMed. PMID: 29479654.
49. Melchionda V, Harman KE. Pemphigus vulgaris and pemphigus foliaceus: an overview of the clinical presentation, investigations, and management. Clinical and Experimental Dermatology. Blackwell Publishing Ltd. 2019 Oct; 44(7): 740–746. PubMed. PMID: 31378971.
50. Tavakolpour S. Pemphigus trigger factors: special focus on pemphigus vulgaris and pemphigus foliaceus. Archives of Dermatological Research. SpringerVerlag. 2018 Mar; 310(2): 95–106. PubMed. PMID: 29110080.
51. Di Lernia V, Casanova DM, Goldust M, Ricci C. Pemphigus Vulgaris and Bullous Pemphigoid: Update on Diagnosis and Treatment. Dermatol Pract Concept. 2020 Jun; 10(3): e2020050. PubMed. PMID: 32642305.
52. Gregoriou S, Efthymiou O, Stefanaki C, Rigopoulos D. Management of pemphigus vulgaris: Challenges and solutions. Clinical, Cosmetic and Investigational Dermatology. Dove Medical Press Ltd. 2015; 8: 521–7. PubMed. PMID: 26543381.
53. Santi CG, Gripp AC, Roselino AM, Mello DS, Gordilho JO, de Marsillac PF, et al. Consensus on the treatment of autoimmune bullous dermatoses: Bullous pemphigoid, mucous membrane pemphigoid, and epidermolysis bullous acquisita – Brazilian society of dermatology. An Bras Dermatol. 2019 Mar;94(2 Suppl 1):33-47. PubMed.PMID: 31166405.
54. Chan LS, Ahmed AR, Anhalt GJ, Bernauer W, Cooper KD, Elder MJ, et al. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators, Arch Dermatol. 2002 Mar; 138(3):370-9. PubMed. PMID: 11902988.
55. Fleming TE, Korman NJ. Cicatricial pemphigoid. Journal of the American Academy of Dermatology. Mosby Inc.2000 Oct; 43(4):571-91.PubMed. PMID:11004612.

56. Setterfield J, Shirlaw PJ, Kerr-Muir M, Neill S, Bhogal BS, Morgan P, et al. Mucous membrane pemphigoid: a dual circulating antibody response with IgG and IgA signifies a more severe and persistent disease. Br J Dermatol. 1998 Apr;138(4):602-10. PubMed. PMID: 9640363.
57. Alpsoy E, Arman-Karakas A, Unzun S. Geographic variations in epidemiology of two autoimmune bullous diseases: pemphigus and bullous pemphigoid. Arch Dermatol Res. 2015 May;307 (4):291-8. PubMed. PMID: 25589418.
58. Gotter, A. and Collins, D., 2022. Everything You Need to Know About Corticosteroids. [Internet] Healthline. [cited 22 March 2022]. Available from https://www.healthline.com/health/corticosteroids-what-are-they
59. Williams DM. Clinical pharmacology of corticosteroids. Respir Care. 2018 Jun;63(6):655–70. PubMed. PMID: 29794202.
60. Ghosh A, Coondoo A. Systemic side effects of topical corticosteroids. In: A Treatise on Topical Corticosteroids in Dermatology: Use, Misuse and Abuse. Springer Singapore. 2017 Sep-Oct; 59(5): 460-464. PubMed. PMID: 25284850.
61. Takeda K, Arase S, Takahashi S. Side Effects of Topical Corticosteroids and their Prevention. Drugs. 1988; 36 (Suppl 5):15-23. PubMed. PMID: 3076129.
62. Mori M, Pimpinelli N, Giannotti B. Topical Corticosteroids and Unwanted Local Effects Improving the Benefit-Risk Ratio. Drug Saf. 1994 May; 10(5): 406-12. PubMeed. PMID: 8037890.
63. Brazzini B, Pimpinelli N. New and Established Topical Corticosteroids in Dermatology Clinical Pharmacology and Therapeutic Use. Am J Clin Dermatol. 2002; 3(1): 47-58. PubMed. PMID: 11817968.
64. Mehta A, Nadkarni NJ, Patil SP, Godse K V., Gautam M, Agarwal S. Topical corticosteroids in dermatology. Indian Journal of Dermatology, Venereology and Leprology. Medknow Publications.2016 Jul-Aug; 83(4):371-8. PubMed. PMID: 27279294.
65. Katz M, Gans EH. Topical Corticosteroids, Structure-Activity and the Glucocorticoid Receptor: Discovery and Development—A Process of "Planned Serendipity. J Pharm Sci. 2008 Aug;97(8):2936–47. PubMed. PMID: 17975808.
66. Rousseau GG, Schmit JP. Structure-activity relationship for glucocorticoids-I: Determination of receptor binding and biological activity. J Steroid Biochem. 1977 Sep;8(9);911-9. PubMed. PMID: 199797.

67. Burkholder B. Topical corticosteroids: An update. Curr Probl Dermatol. 2000;12(5):222-5.
68. Schimmer BP, Funder JW. Chapter 42. ACTH, Adrenal Steroids, and Pharmacology of the Adrenal Cortex. Goodman Gilman's Pharmacology Basis Ther 123. 2011;1(Chapter 18):1-30
69. Goa KL. Clinical Pharmacology and Pharmacokinetic properties of Topically Applied Corticosteroids. Drugs. 1988;36(Suppl5):51-61. PubMed. PMID: 3076132.
70. Yohn J, Weston WL. Topical glucocorticosteroids. Curr Probl Dermatol. 1990;2:31-
71. Mori M, Pimpinelli N, Giannotti B. Topical corticosteroids and unwanted local effects. Improving the benefit/risk ratio. Drug Saf 1994 May; 10(5):406-12. PubMed. PMID: 8037890
72. Miller JA, Munro DD. Topical Corticosteroids: Clinical Pharmacology and Therapeutic Use. Drugs. 1980 Feb;19(29;119-34. PubMed. PMID: 7363838.
73. WHO model prescribing information: drugs used in skin diseases: Annex: Classification of topical corticosteroids. [Internet] [cited 10 April 2022]. Available from: http://apps.who.int/medicinedocs/en/d/ Jh2918e/32.html#Jh2918e.32.
74. British National Formulary (BNF). 69th ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; March 2015.
75. Scoggins RB, Kliman B. Relative potency of percutaneously absorbed corticosteroids in the suppression of pituitary-adrenal function. J Invest Dermatol 1965 Nov;45(5): 347-55. PubMed. PMID:5321337.
76. Hengge UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of topical glucocorticosteroids. Journal of the American Academy of Dermatology. Mosby. Inc.2006 Jan;54(1):1-15. PubMed. PMID: 16384751.
77. Ponec M, Kempenaar JA, De Kloet ER. Corticoids and cultured human epidermal keratinocytes: specific intracellular binding and clinical efficacy. J Invest Dermatol. 1981 Marc;76(3):211–4. PubMed. PMID: 6165779.
78. Marks R, Barlow JW, Funder JW. Steroid-induced vasoconstriction: glucocorticoid antagonist studies. J Clin Endocrinol Metab. 1982 May;54(5):1075–7. PubMed. PMID: 7061698.
79. Schacke H, Rehwinkel H, Asadullah K, Cato ACB. Insight into the molecular mechanisms of glucocorticoid receptor action promotes identification of novel ligands with an improved therapeutic index. Exp Dermatol. 2006 Aug;15(8):565-73. PubMed. PMID: 16842594.

80. Sibila O, Suarez-cuartin G, Rodrigo-troyano A, Anzueto A. Corticosteroids and Pneumonia in Chronic Obstructive Pulmonary Disease: A Dual Effect ? Barcelona Respir Netw 2015 Oct 1;1(2):105-15. Research Gate. doi: 10.23866/BRNRev:2015-0010
81. Altura B. Role of glucocorticosteroids in local regulation of blood flow. Am J Physiol Content. 1966 Dec 1;211(6):1393–7. PubMed. PMID: 5956555.
82. Christophers E, Schopf E, Kligman AM, et al., editors. Topical corticosteroid therapy: a novel approach to safer drugs. New York, NY: Raven Press; 1988:57–65.
83. Giannotti B, Pimpinelli N. Topical Corticosteroids. Drugs. 1992 Jul;44(1):65–71.
84. Van der Vleuten CJ, Van Vlijmen IM, De Jong EM, et al. Clobetasol-17 propionate lotion under hydrocolloid dressing (Duoderm ET) once weekly versus un- occluded clobetasol- 17 propionate ointment twice daily in psoriasis: an immunohistochemical study on remission and relapse. Arch Dermatol Res 1999 Jul- Aug; 291 (7-8): 390-5. PubMed. PMID: 10482007.
85. Lagos BR, Maibach AI. Frequency of application of topical corticosteroids: an overview.Br J Dermatol 1998 Nov 4;139(5):763–6. PubMed. PMID: 9892939.
86. Li VC, Chowdhury MM. Dermatological pharmacology topical agents. Medicine (United Kingdom). Elsevier Ltd; 2017. 45: 359-62. PubMed. doi: https://doi.org/10.1016/j.mpmed.2021.03.003
87. Rosen J, Landriscina A, Friedman AJ. Principles and approaches for optimizing therapy with unique topical vehicles. J Drugs Dermatol. 2014 Dec;13(12):1431–5.PubMed. PMID: 25607783.
88. Buhse, , Kolinski R, Benjamin Westenberger B, Wokovich A, et al. Topical drugclassification. International journal of pharmaceutics. 2005 May; 295(1-2):101-12.PubMed. 15847995.
89. Freepik. 2022. Ointment | Free Download. [Internet]. Available at: https://stock.adobe.com/pt/search?filters%5Bcontent_type%3Aphoto%5D=1&filters%%205Bcontent_type%3Aillustration%5D=1&filters%5Bcontent_type%3Azip_vector%5%20D=1&filters%5Bcontent_type%3Avideo%5D=1&filters%5Bcontent_type%3Atemplat%20e%5D=1&filters%5Bcontent_type%3A3d%5D=1&filters%5Bcontent_type%3Aimage%5D=1%20&k=ointment&order=relevance&safe_search=1&limit=100&search_page=1&%20search_type=usertyped&acp=&aco=ointment &get_facets=0 [cited 30 May 2022]

90. Freepik. 2022. Cream | Free Download. [Internet]. Available at: https://br.freepik.com/search?format=search&query=cream%20 [cited 30 May2022].
91. Freepik. 2022. Cream | Free Download. [Internet]. Available at: https://br.freepik.com/search?format=search&query=lotion [cited 30 May 2022].
92. Freepik. 2022. Espuma Medicamento | Free Download. [Internet]. Available at: https://stock.adobe.com/pt/search?filters%5Bcontent_type%3Aphoto%5D=1&filters%5%20Bcontent_type%3Aillustration%5D=1&filters%5Bcontent_type%3Azip_vector%5%20D=1&filters%5Bcontent_type%3Avideo%5D=1&filters%5Bcontent_type%3Atemplat%20e%5D=1&filters%5Bcontent_type%3A3d%5D=1&filters%5Bcontent_type%3Aimage%5D=1%20&k=espuma+medicamento&order=relevance&safe_search=1&limit=100&sear%20ch_page=1&search_type=usertyped&acp=&aco=espuma+medicamento&get_facets=0%20&asset_id=329087251 [cited 30 May2022].
93. Freepik. 2022. Lotion | Free Download. [Internet]. Available at: https://br.freepik.com/search?format=search&query=lotion [cited 30 May 2022].
94. Robertson DB, Maibach HI. Topical corticosteroids. Int J Dermatol 1982 March;21 (2):59-67. Wiley Online Library. doi: **https://doi.org/10.1111/j.1365-4362.1982.tb00498.x**
95. Coondoo A, Phiske M, Verma S, Lahiri K. Side-effects of topical steroids: A long overdue revisit. Indian Dermatol Online J. 2014 Oct;5(4):416. PubMed. PMID: 25396122.
96. Stoughton RB, Cornell RL: Review of super-potent topical corticosteroids. Semin Dermatol 1987;6 (2):72-76. Google Scholar
97. Abraham A, Roga G. Topical steroid-damaged skin. Indian J Dermatol. 2014 Sep;59(5):456-9. PubMed. PMID: 25284849.
98. Fisher DA. Adverse effects of topical corticosteroid use. West J Med 1995 Feb;162 (2):123-6. PubMed. PMID: 7794369.
99. Warner MR, Camisa C. Topical corticosteroids. In: Wolverton SE, editor. Comprehensive dermatologic drug therapy. 3rd ed. New York, NY.Elsevier Health.:487– 504.
100. Stamatas GN, Nikolovski J, Mack MC, Kollias N. Infant skin physiology and development during the first years of life: a review of recent findings based on in vivo studies. Int J Cosmet Sci. 2011 Feb;33(1):17–24. PubMed. PMID: 20807257.

101. Couturaud V, Coutable J, Khaiat A. Skin biomechanical properties: in vivo evaluation of influence of age and body site by a non-invasive method. Skin Res Technol. 1995 May;1(2):68–73. PubMed. PMID: 27328385.
102. Bewley A. Expert consensus: Time for a change in the way we advise our patients to use topical corticosteroids. In British Journal of Dermatology. 2008 May;158(5):917–20. PubMed. PMID: 18294314.
103. Yancey KB. Management of mucous membrane pemphigoid. [Internet]. 2022.Available from: https://www.update.com/contents/mangement-of-mucous-membrane-pemphigoid-
104. Hertl M, Geller S. Initial management of pemphigus vulgaris and pemphigus foliaceus [Internet]. 2022. Available from: https://www.uptodate.com/contents/initial-management-of-pemphigus-vulgaris-and-pemphigusfoliaceus?search=pemphigus&source=search_result&selectedTitle=2~88&usage_type=default&display_rank
105. Mirowski GW, Schlosser Bj, Oral lichen planus: Management and prognosis [Internet]. 2022. Available from: https://www.uptodate.com/contents/oral-lichen-planus-management-andprognosis?search=oral%20licheen&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
106. Prednisolone: Uses, Interactions, Mechanism of Action | Drug Bank Online [Internet]. Go.drugbank.com. 2022 [cited 5 April 2022]. Available from: https://go.drugbank.com/drugs/DB00860
107. Infomed - Prednisolona [Internet]. Extranet.infarmed.pt. 2022 [cited 5 April 2022]. Available from: https://extranet.infarmed.pt/INFOMED-fo/pesquisa- avancada.xhtml
108. Prednisolone. In: In Depth Answers [database on the Internet]. Greenwood Village (CO): IBM Corporation; [cited 2022 April 5]. Available from: www.micromedexsolutions.com. Subscription required to view
109. Methylprednisolone: Uses, Interactions, Mechanism of Action | DrugBank Online [Internet]. Go.drugbank.com. 2022 [cited 5 April 2022]. Available from: https://go.drugbank.com/drugs/DB00959
110. Infomed - Metilprednisolona [Internet]. Extranet.infarmed.pt. 2022 [cited 5 April 2022]. Available from: https://extranet.infarmed.pt/INFOMED-fo/pesquisa-avancada.xhtml

111. Methylprednisolone. In: In Depth Answers [database on the Internet]. Greenwood Village (CO): IBM Corporation; [cited 2022 April 5]. Available from: www.micromedexsolutions.com. Subscription required to view
112. Dexamethasone: Uses, Interactions, Mechanism of Action | DrugBank Online [Internet]. Go.drugbank.com. 2022 [cited 5 April 2022]. Available from: https://go.drugbank.com/drugs/DB0
113. Infomed - Dexametasona [Internet]. Extranet.infarmed.pt. 2022 [cited 5April2022]. Available from: https://extranet.infarmed.pt/INFOMED-fo/pesquisa- avancada.xhtml
114. Dexametasone. In: In Depth Answers [database on the Internet]. Greenwood Village (CO): IBM Corporation; [cited 2022 April 5]. Available from: www.micromedexsolutions.com. Subscription required to view.
115. Betamethasone: Uses, Interactions, Mechanism of Action | DrugBank Online [Internet]. Go.drugbank.com. 2022 [cited 5 April 2022]. Available from: https://go.drugbank.com/drugs/DB00443
116. Infomed - Betametasona [Internet]. Extranet.infarmed.pt. 2022 [cited 5 April 2022]. Available from: https://extranet.infarmed.pt/INFOMED-fo/pesquisa-avancada.xhtml
117. Betamethasone. In: In Depth Answers [database on the Internet]. Greenwood Village (CO): IBM Corporation; [cited 2022 April 5]. Available from: www.micromedexsolutions.com. Subscription required to view
118. Hydrocortisone: Uses, Interactions, Mechanism of Action | DrugBank Online [Internet]. Go.drugbank.com. 2022 [cited 5 April 2022]. Available from: https://go.drugbank.com/drugs/DB00741
119. Infomed – Hidrocortisona [Internet]. Extranet.infarmed.pt. 2022 [cited 5April 2022]. Available from: https://extranet.infarmed.pt/INFOMED-fo/pesquisa-avancada.xhtml
120. Hydrocortisone. In: In Depth Answers [database on the Internet]. Greenwood Village (CO): IBM Corporation; [cited 2022 April 5]. Available from: www.micromedexsolutions.com. Subscription required to view
121. Budesonide: Uses, Interactions, Mechanism of Action | DrugBank Online [Internet]. Go.drugbank.com. 2022 [cited 5 April 2022]. Available from: https://go.drugbank.com/drugs/DB01222
122. Infomed - Budesonide [Internet]. Extranet.infarmed.pt. 2022 [cited 5 April 2022]. Available from: https://extranet.infarmed.pt/INFOMED-fo/pesquisa-avancada.xhtml

123. Budesonide. In: In Depth Answers [database on the Internet]. Greenwood Village (CO): IBM Corporation; [cited 2022 April 5]. Available from: www.micromedexsolutions.com. Subscription required to view

124. Clobetasol Propionate: Uses, Interactions, Mechanism of Action | DrugBank Online [Internet]. Go.drugbank.com. 2022 [cited 5 April 2022]. Available from: https://go.drugbank.com/drugs/DB01013

125. Infomed – Propionato de Clobetasol [Internet]. Extranet.infarmed.pt. 2022 [cited 5 April 2022]. Available from: https://extranet.infarmed.pt/INFOMED- fo/pesquisa-avancada.xhtml

126. Clobetasol Propionate. In: In Depth Answers [database on the Internet]. Greenwood Village (CO): IBM Corporation; [cited 2022 April 5]. Available from: www.micromedexsolutions.com. Subscription required to view

127. Fluticasone: Uses, Interactions, Mechanism of Action | DrugBank Online [Internet]. Go.drugbank.com. 2022 [cited 5 April 2022]. Available from: https://go.drugbank.com/drugs/DB13867

128. Infomed - Fluticasona [Internet]. Extranet.infarmed.pt. 2022 [cited 5 April 2022]. Available from: https://extranet.infarmed.pt/INFOMED-fo/pesquisa- avancada.xhtml

129. Fluticasone.. In: In Depth Answers [database on the Internet]. Greenwood Village (CO): IBM Corporation; [cited 2022 April 5]. Available from: www.micromedexsolutions.com. Subscription required to view

130. Triamcinolone: Uses, Interactions, Mechanism of Action | DrugBank Online [Internet]. Go.drugbank.com. 2022 [cited 5 April 2022]. Available from: https://go.drugbank.com/drugs/DB00620

131. Infomed – Triamcinolona [Internet]. Extranet.infarmed.pt. 2022 [cited 5 April 2022]. Available from: https://extranet.infarmed.pt/INFOMED-fo/pesquisa-avancada.xhtml

132. Triamcinolone. In: In Depth Answers [database on the Internet]. Greenwood Village (CO): IBM Corporation; [cited 2022 April 5]. Available from: www.micromedexsolutions.com. Subscription required to view

133. Beclomethasone: Uses, Interactions, Mechanism of Action | DrugBank Online [Internet]. Go.drugbank.com. 2022 [cited 5 April 2022]. Available from: https://go.drugbank.com/drugs/DB00394

134. Infomed - Beclometasona [Internet]. Extranet.infarmed.pt. 2022 [cited 5April 2022]. Available from: https://extranet.infarmed.pt/INFOMED-fo/pesquisa-avancada.xhtml

135. Beclomethasone. In: In Depth Answers [database on the Internet]. Greenwood Village (CO): IBM Corporation; [cited 2022 April 5]. Available from: www.micromedexsolutions.com. Subscription required to view
136. Fluocinolone acetonide: Uses, Interactions, Mechanism of Action | DrugBank Online [Internet]. Go.drugbank.com. 2022 [cited 5 April 2022]. Available from: https://go.drugbank.com/drugs/DB00591
137. Infomed – Acetonido de Fluocinolona [Internet]. Extranet.infarmed.pt. 2022 [cited 5 April 2022]. Available from: https://extranet.infarmed.pt/INFOMED- fo/pesquisa-avancada.xhtml
138. Fluocinolone acetonide. In: In Depth Answers [database on the Internet]. Greenwood Village (CO): IBM Corporation; [cited 2022 April 5]. Available from: www.micromedexsolutions.com. Subscription required to view
139. Desonide: Uses, Interactions, Mechanism of Action | DrugBank Online [Internet]. Go.drugbank.com. 2022 [cited 5 April 2022]. Available from: https://go.drugbank.com/drugs/DB01260
140. Infomed - Desonida [Internet]. Extranet.infarmed.pt. 2022 [cited 5 April 2022]. Available from: https://extranet.infarmed.pt/INFOMED-fo/pesquisa- avancada.xhtml
141. Infomed - Desonida [Internet]. Extranet.infarmed.pt. 2022 [cited 5 April 2022]. Available from: https://extranet.infarmed.pt/INFOMED-fo/pesquisa- avancada.xhtml
142. Mometasone: Uses, Interactions, Mechanism of Action | DrugBank Online [Internet]. Go.drugbank.com. 2022 [cited 5 April 2022]. Available from: https://go.drugbank.com/drugs/DB00764
143. Infomed - Mometasona [Internet]. Extranet.infarmed.pt. 2022 [cited 5 April 2022]. Available from: https://extranet.infarmed.pt/INFOMED-fo/pesquisa- avancada.xhtml
144. Mometasone. In: In Depth Answers [database on the Internet]. Greenwood Village (CO): IBM Corporation; [cited 2022 April 5]. Available from: www.micromedexsolutions.com. Subscription required to view
145. García-Pola MJ, González-Álvarez L, Garcia-Martin JM. Tratamiento del liquen plano oral. Revisión sistemática y protocolo de actuación. Med Clin (Barc). 2017 Oct;149(8):351–62. PubMed. doi: 10.1016/j.medcli.2017.06.024
146. Harman KE, Albert S, Black MM. Guidelines for the management of pemphigus vulgaris. Br J Dermatol. 2003 Nov;149(5):926–37. PubMed. PMID: 14632796.

147. Joly P, Horvath B, Patsatsi, Uzun S, Bech R, Beissert S, et al. Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the European academy of dermatology and venereology (EADV). J Eur Acad Dermatology Venereol. 2020 Sep;34(9):1900– 13. PubMed. PMID: 32830877.

148. Schmidt E, Rashid H, Marzano A V., Lamberts A, Di Zenzo G, Diercks GFH, et al. European Guidelines (S3) on diagnosis and management of mucous membrane pemphigoid, initiated by the European Academy of Dermatology and Venereology – Part II. J Eur Acad Dermatology Venereol. 2021 Oct;35(10):1926– 48. PubMed. PMID: 34309078.

149. Taylor J, McMillan R, Shephard M, Setterfield J, Ahmed R, Carrozzo M, et al. World Workshop on Oral Medicine VI: A systematic review of the treatment of mucous membrane pemphigoid. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015 Aug;120(2):161-171.e20. PubMed. PMID: 25953640.

150. AusDI. St Leonards, N.S.W. ;: Phoenix Medical Publishing; 2012.

151. Wockhardt Pharmaceuticals. Baycadron TM Elixir 0.5 mg/5 mL dexamethasone USP Product Information Leaflet [Internet]. Elvesier Health. 2012 [cited 30 April 2022]. Available from: https://elsevier.health/en- US/preview/dexamethasone

152. Rosemont Pharmacetuicals. Dexsol" 2 mg/ 5 ml Oral Solution Dexamethasone Sodium Phosphate Patient Information Leaflet [Internet]. Datapharm. 2010 [cited 30 April 2022]. Available from: https://www.medicines.org.uk/emc/

153. BI Pharmaceuticals Inc Roxane Laboratories. Intensol TM Dexamethasone Oral solution 1 mg/1 mL Product Information Leaflet. 2010 [cited 30 April 2022]. Available from:https://webcache.googleusercontent.com/search?q=cache:G9C8CnWgNbUJ:https://docs.boehringeringelheim.com/Prescribing%2520Information/PIs/Roxane/Dexamethasone/Dexamethasone%2520Tablets%2520Solution%2520and%2520Intensol.pdf+&cd=1&hl=ptPT&ct=clnk&gl=pt&client=safari

154. Le Cleach L, Chosidow O. Clinical Practice. Lichen Planus. N Engl J Med. 2012 Feb;366(8):723–32. PubMed. PMID: 22356325.

155. Rhodus NL, Cheng B, Bowles W, Myers S. Miller L, Ondrey F. Proinflammatory cytokine levels in saliva before and after treatment of (erosive) oral lichen planus with dexamethasone, Oral Dis 2006 Mar; 12 (2); 112-6. PubMed. PMID: 16476030.

156. Hamishehkar H, Nokhodchi a, Ghanbarzadeh S, Kouhsoltani M. Triamcinolone acetonide or mucoadhesive paste for treatment of aphthousstomatitis. Adv Pharm Bull. 2015 Jun; 5(2): 277- 82. PubMed. PMID: 26236668.

157. Said Z, Murdoch C, Hansen J, Siim Madsen L, Colley HE. Corticosteroid delivery using oral mucosa equivalents for the treatment of inflammatory mucosal diseases. Eur J Oral Sci. 2021 Apr ;129(2):e12761. PubMed. PMID: 33645844.

158. Caro V De Sutera FM, Giannola LI. In situ delivery of corticosteroids for treatment of oral diseases. Therapeutic Delivery. Future Medicine Ltd.;2017 Oct; 8(19):899-914. PubMed. PMID: 28944742.

159. Hearnden V, Sankar V, hull K, Juras Dv, Greenberg M, Kerr Ar, er al, New developments and opportunities in oral mucosal drug delivery for local and systemic disease. Advanced Drug Delivery Reviews. 2012 Jan; 64(1):16-28. PubMed. PMID: 21371513.

160. Paderni C, Compilato D, Giannola LI, Campisi G. Oral local drug delivery and new perspectives in oral drug formulation. Oral Surg Oral Med Oral PatholOral Radiol. 2012 Sep;114(3):e25–34. PubMed. PMID: 22771408.

161. Nguyen S, Hiorth M. Advanced drug delivery systems for local treatment of the oral cavity. Therapeutic Delivery. Future Science Ltd; 2015;6(5): 595-608.PubMed. PMID: 26001175.

162. Venkatalaskshmi R, Sudhakar Y, Chetty C. M, Sasikala C, Mohan VarmaM. Buccal Drug Delivery Using Adhesive Polumeric Patches. Int J PharmSci Res. 2012 Jan;5:35–4. International Journal of Pharmaceutical Sciences and Research. Doi: http://dx.doi.org/10.13040/IJPSR.0975-8232.3(1).35-41

163. Woodley J. Bioadhesion: new possibilities for drug administration ? Clin Pharmacokinetic. 2001;40(2):77–84. PubMed. PMID: 11286325.

164. Mishra P.R, Nameeo A, Jain, S, Jain N.K. Hydrogels as drug deliverysystem, Indian Drugs ;1996;43(4). 181.186

165. Nazar H, Roldo M, Fatouros DG, van der Merwe SM, Tsibouklis J. Hydrogels in mucosal delivery. Ther Deliv. 2012 Apr;3(4):535–55. PubMed. PMID: 22834081.

166. Mendes AI, Silva AC, Catita JAM, Cerqueira F, Gabriel C, Lopes CM. Miconazole-loaded nanostructured lipid carriers (NLC) for local delivery to the oral mucosa: Improving antifungal activity. Colloids Surfaces B Biointerfaces. 2013 Nov;111:755–63. PubMed. PMID: 23954816

167. Alsarra IA, Alanazi FK, Mahrous GM, Abdel Rahman AA, Al Hezaimi KA.Clinical evaluation of novel buccoadhesive film containing ketorolac in dental and post-oral surgery pain management. Pharmazie. 2007 Oct;62(10):773–8. PubMed. PMID: 18236783.

168. Save T, Shah MU, Ghamande AR, Venkitachalam P. Comparative Study of Buccoadhesive Formulations and Sublingual Capsules of Nifedipine. J Pharm Pharmacol. 2011 Apr 12;46(3):192–5. PubMed. PMID: 8027926.

169. Bensadoun R-J, Daoud J, El Gueddari B, Bastit L, Gourmet R, Rosikon A, et al. Comparison of the efficacy and safety of miconazole 50-mg mucoadhesive buccal tablets with miconazole 500-mg gel in the treatment of oropharyngeal candidiasis. Cancer. 2008 Jan 1;112(1):204–11. PubMed. PMID: 18044772.

170. Ali J, Khar RK, Ahuja A. Formulation and characterisation of a buccoadhesive erodible tablet for the treatment of oral lesions. Pharmazie. 1998 May;53(5):329–34. PubMed. PMID: 9631501.

171. Innocenti M, Moscatelli G, Lopez S. Efficacy of Gelclair in Reducing Pain in Palliative Care Patients with Oral Lesions. J Pain Symptom Manage. 2002 Nov;24(5):456–7. PubMed. PMID: 12547044

172. Javaid MU, Shahid S. Buccal Patches: An Advanced Route of Drug Dosage Delivery - A Review. 2017 Oct;10 (3):206–2016. International Journal of Pharmacy & Pharmaceutical Research. ISSN 2349-7203.

173. Puratchikody A, Prasanth V, Mathew S, Ashokkumar B. Buccal Drug Delivery: Past, Present and Future - A Review. Int Jourrnal Drug Deliv. 2011Jan;3(2):171–84. Research Gate.

174. Batchelor H. Novel bioadhesive formulations in drug delivery, The Drug Delivery Companies Report Autumn/Winter, Pharma Ventures Ltd.2004;2(5):109- 114.Science and Education. doi: 10.12691/ajmsm-2-5-5.

175. Pramodkumar TM, Shivakumar HG, Desai K. Oral transmucosal drug delivery systems. Indian Drugs. 2004 Feb;41 (2):63–75.

176. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: a review.J Pharm Pharm Sci. 1998 Jan-apr;1(1):15–30. PubMed. PMID: 10942969.

177. K.P.R. Chowdhary and L.Shrinivas. Mucoadhesive Drug Delivery Systems: A review of Current Status, Indian Drugs, Sep 2000, 37(9), 400-406.

178. Harding SE, Davis SSB, Deacon MP, Fiebrig I. Biopolymer Mucoadhesives. Biotechnol Genet Eng Rev. 1999 Apr;16(1):41–86. PubMed. PMID: 10819077.

179. METIA PK, BANDYOPADHYAY AK. In Vitro Evaluation of or a Mucoadhesive Buccal Tablet of Oxytocin Prepared with Diospyros Peregrina Fruits Mucilages. YAKUGAKU ZASSHI. 2008 Apr ;128(4):603–9. PubMed. PMId: 18379177.

180. TANABE M, WATANABE M, YANAGI M, NISHIZAWA S, CHIGONO Y, MATSUDA J, et al. Controlled Indomethacin Release from Mucoadhesive Film: In vitro and Clinical Evaluations. YAKUGAKU ZASSHI. 2008 Nov;128(11):1673– 9. PubMed. PMID: 18981703.

181. Malik DK, Baboota S, Ahuja A, Hasan S, Ali. Recent advances in proteinand peptide drug delivery systems. J Curr Drug Deliv 2007 Apr;4(2):141-151. PubMed. PMID:17456033.

182. SALAMATMILLER N, CHITTCHANG M, JOHNSTON T. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliv Rev. 2005 Nov 3;57(11):1666–91. Pubmed. PMID: 16183164.

183. Sayani AP, Chien YW. Systemic delivery of peptides and proteins across absorptive mucosae. Crit Rev Ther Drug Carrier Syst. 1996;13(1–2):85–184. PubMed. PMID: 8853960.

184. MIYAZAKI S, NAKAYAMA A, ODA M, TAKADA M, ATTWOOD D. Chitosan and Sodium Alginate Based Bioadhesive Tablets for Intraoral Drug Delivery. BiolPharm Bull. 1994 May;17(5):745–7. PubMed. PMID: 7920448.

185. Ceschel GC, Maffei P, Borgia SL. Design and evaluation of a new Mucoadhesive bilayered tablet containing nimesulide for buccal administration.Drug Deliv 2004 Jul-Aug;11(4):225-230.PubMed. PMID: 15371103.

186. Remunan-lopez C, Portero A, Vila-Jato JL Alonso MJ. Design and evaluation of chitosan/ethyl cellulose mucoadhesive bilayered devices for Buccal drug delivery. J. Control. Release 1998 Nov;55(2-3):143-152. PubMed. PMID:9795035.

187. Abuja A, Khar RK, Ali J. Mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm 1997;23(5):489-517.Taylor & Francis Online. doi: https://doi.org/10.3109/03639049709148498

188. Nagai T. Adhesive topical drug delivery system. J Control Release. 1985 Nov;2:121–34. Science Direct. doi: https://doi.org/10.1016/0168-3659(85)90038-0

189. Ceschel GC, Maffei P, Lombar S. Design and Evaluation of Buccal Adhesive Hydrocortisone Acetate (HCA) Tablets. Drug Deliv. 2001 Jul-Aug ;8(3):161–71. PubMeed. PMID: 11570597.

190. Rafiee-Tehranu M, Jazayeri G, Toliyat T, Bayati K, Khalkhali K, Shamimi K, Miremadi A, Dorkoosh FA. Development and intro-vitro evaluation of novel bucoadhesive tablet formulation of prednisolone, Acta Pharm 2002;52:123-130.

191. Nagai T, Konishi R. Buccal/gingival drug delivery systems. J Control Release. 1987 Dec;6(1):353–60.

192. Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery — A promising option for orally less efficient drugs. J Control Release. 2006 Aug;114(1):15–40. PubMed. PMID: 16828915.

193. Keegan GM, Smart JD, Ingram MJ, Barnes L-M, Burnett GR, Rees GD.Chitosan microparticles for the controlled delivery of fluoride. J Dent. 2012 Mar;40(3):229–40. PubMed. PMID: 22212236.

194. Akbarzadeh A, Rezaei-Sadabady R, Davaran S, Joo SW, Zarghami N, Hanifehpour Y, et al. Liposome: classification, preparation, and applications. Nanoscale Res Lett. 2013 Dec 22;8(1):102. PubMed. PMID: 23432972.

195. Harsanyi BB, Hilchie JC, Mezei M. Liposomes as Drug Carriers for Oral Ulcers. J Dent Res. 1986 Sep;65(9):1133–41. PubMed. PMID: 3461030.

196. Discher DE, Ortiz V, Srinivas G, Klein ML, Kim Y, Christian D, et al. Emerging applications of polymersomes in delivery: From molecular dynamics to shrinkage of tumors. Prog Polym Sci. 2007 Aug;32(8–9):838–57. PubMed. PMID: 24692840.

197. Farshi F.S, Ozer A.Y, Ercan M.T, Hincal A.A. In-vivo studies in the treatment of oral ulcers with liposomal dexamethasone sodium phosphate. J Microencapsul. 1996 Oct;13(5)537-544. PubMed. PMID: 8864991.

198. Bendas E.R, Abdullah H, El-Komy M.H, Kassen M.A. Hydroxychloroquine niosomes: a new trend in topical management of oral lichen planus. Int. J. Pharm. 2013 Dec; 458(2):287-295. PubMed. PMId: 24184035.

199. Save T, Shah MU, Ghamande AR, Venkitachalam P. Comparative Study of Buccoadhesive Formulations and Sublingual Capsules of Nifedipine. J Pharm Pharmacol. 2011 Apr 12;46(3):192–5. PubMed. PMID: 8027926.

200. Shojaei AH, Li X, Mechanisms of buccal mucoadhesion of novel copolymers or acrylic acid and polyethylene glycol monomethyether monomethacrylate. J Control Release 1997 Aug;47(2):151-161. Science Direct. doi: https://doi.org/10.1016/S0168-3659(96)01626-4

201. Azizi A, Dadras OG, Jafari M, Moezi Ghadim N, Lawaf S, Sadri D. Efficacy of 0.1% triamcinolone with nanoliposomal carrier formulation in orabase for oral lichen planus patients: A clinical trial. Eur J Integr Med. 2016 Jun;8(3):275–80. Science Direct. doi: https://doi.org/10.1016/j.eujim.2015.09.138

202. New biodegradable hydrogel offers eco-friendly alternative to synthetics [Internet]. Ece.engin.umich.edu. 2022 [cited 30 May 2022]. Available from: https://ece.engin.umich.edu/stories/new-biodegradable-hydrogel-offers-eco- friendly-alternative-to-synthetics/

203. Geomatrix® technology by Skyepharma - Multi-layer tablet [Internet]. Skyepharma. 2022 [cited 30 May 2022]. Available from: https://www.skyepharma.com/geomatrix/

204. Goap S, SaiArchana P, Ammal M. Oral Bio Dissolving Films in Dentistry: A new perspective in treatment modality. 2015

205. Shanker G, Kumar CK, Gonugunta CS, Kumar BV, Veerareddy PR. Formulation and evaluation of bioadhesive buccal drug delivery of tizanidine hydrochloride tablets. AAPS PharmSciTech. 2009;10(2):530-9. PMID: 19424804.

206. Irache J, Huici M, Konecny M, Espuelas S, Campanero M, Arbos P. Bioadhesive Properties of Gantrez Nanoparticles. Molecules2005 Jan;10(1):126-45. PubMed. PMID: 18007282.

207. Liposome-based drug products - Q&A - Materials Talks [Internet]. Materials Talks. 2022 [cited 30 May 2022]. Available from: https://www.materials-talks.com/liposome-based-drug-product-deformulation-and-characterization/