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REVIEW
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A 10-Year Observational Study on Treatment Approaches in Pemphigus and Pemphigoid

Desetogodišnja opservacijska studija o pristupima liječenju pemfigusa i pemfigoida

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Abstract

Objectives: The aim of this study was to evaluate epidemiological data on pemphigus vulgaris and pemphigoid, with special focus on characteristics, clinical manifestations, and treatment approaches. **Materials and methods:** This study includes patients who have been diagnosed with pemphigus vulgaris or pemphigoid at the Dermatology Service of the Santa Maria Local Health Unit between the years 2013 and 2022. The statistical software IBM SPSS® version 29, with Clopper-Pearson 95% confidence intervals (CI) was used for proportions. **Results:** The total number of patients included in this study is 99 patients with pemphigus vulgaris (49 females, 50 males) and 227 with pemphigoid patients (108 females, 119 males). Patients who have been treated for pemphigus vulgaris, the most prescribed medicine were corticosteroids, followed by the second most prescribed, drugs which were immunosuppressants. Additionally rituximab was used in 21 patients. The interval of the disease was 304 days; with an interval of no symptom disease was 415 days for relapsed patients. Similarly, for pemphigoid, the primary treatment used was with corticosteroids, which were also used for the main treatment, in many cases it was combined with other medicines, such as: antihistamines, antibiotics, and immunosuppressants. The average cure time was 148 days, with 32.0% of patients claiming they experienced relapse. **Conclusion:** To conclude, we observed that corticosteroids, particularly prednisolone, remain still the most important pharmacological treatment for pemphigus vulgaris and pemphigoid. However, rituximab is an effective pharmacological alternative for pemphigus, while the use of clobetasol propionate is increasing and becoming as one of the preferred treatments for pemphigoid.

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Introduction

The Autoimmune bullous dermatoses are characterized by blister formation due to autoantibodies targeting intercellular or epithelial-connective junctions (1). There are four variables with autoimmune origin of pemphigus, including: pemphigus vulgaris, pemphigus vegetans, pemphigus erythematosus, and pemphigus foliaceus. Pemphigus vulgaris is the most common subtype and is a mucocutaneous autoimmune blistering disease caused by autoantibodies against desmogleins 1 and 3, which affect the skin and the mucous membranes, including the oral, pharyngeal, laryngeal, esophageal, nasal, conjunctival, and genital mucosa (1-3). Oral lesions may develop further into cutaneous manifesta-

Uvod

Autoimune bulozne dermatoze obilježava stvaranje mjehura zbog autoantitijela usmjerenih na međustanične ili epitelno-vezivne spojeve (1). Četiri su varijable s autoimunim podrijetlom pemfigusa, uključujući pemfigus vulgaris, pemfigus vegetans, pemfigus eritematosus i pemfigus foliaceus. Pemfigus vulgaris najčešći je podtip i mukokutana je autoimuna bolest kod koje se stvaraju mjehuri prouzročeni autoantitijelima protiv desmogleina 1 i 3 koji zahvaća kožu i sluznice, uključujući oralnu, faringealnu, laringealnu, ezofagealnu, nosnu, konjunktivalnu i genitalnu sluznicu (1 – 3). Oralne lezije mogu se dalje razviti u kožne manifestacije i tada je, u većini slučajeva, oralna sluznica prva zahvaćena.

tions, where the oral mucosa is the first one to be affected in most of the cases. The most affected areas in the oral cavity are the palate, labial mucosa, buccal mucosa, ventral tongue, and gingiva, however, other areas of oral cavity might be affected as well (3,4).

Pemphigoid, including bullous pemphigoid, cicatricial pemphigoid, and pemphigoid gestationis, manifest with subepithelial blisters and IgG deposits. Additionally, bullous pemphigoid affects mostly the elderly (those above 60 years old), however, it is very rare seen in children, and thus it has no predisposition for ethnic groups or different biological sexes (1). Clinically, it is characterized by a combination of erythematous macules, papules, and pruritic bullous eruptions. The lesions are mainly widespread, usually symmetrical, and can impact different areas of the skin such as the external areas of the limbs, abdomen, head and neck, and less frequently the mucous membranes and oral mucosa (1-5).

The classical treatment of pemphigus vulgaris contains systemic administration of corticosteroids, with purpose to manage the disease, on the contrary, if left untreated or inadequately managed, the condition can be fatal due to the loss of epidermal barrier function over a large area of skin (3,4,6).

The treatment of the pemphigus vulgaris and pemphigoid diseases might often be challenging. Nowadays, there are recommendations and universal guidelines of treatment, however a standard therapeutic protocol is lacking. Consequently, therapeutic approaches are typically determined by the clinicians, considering the clinical history, age, disease severity, anatomical distribution of lesions, therapeutic response and side effects of the patients (7, 8). To understand whether a treatment requires an immunosuppressive systemic treatment or conservative approach, it is crucial to accurately and early diagnose the autoimmune bullous diseases, considering that usually corticosteroids are the first-line treatment (9, 10). Recent advancements for treatment of bullous autoimmune diseases have introduced targeted therapeutic strategies, including anti-CD20 monoclonal antibodies, bruton tyrosine kinase (BTK) inhibitors, FcRn inhibitors (neonatal Fc receptor blockers), and chimeric autoantibody receptor (CAAR) T-cell therapy for pemphigus vulgaris. The purpose of these new approaches is to modulate the immune response, specifically to offer more potential benefits than traditional therapies. (11-13). On the other hand, for bullous pemphigoid, biologic agents such as dupilumab (IL-4Rα antagonist), omalizumab (anti-IgE monoclonal antibody), and IL-5/eosinophil-targeting therapies are currently being explored. The target specific pathways of the therapies involved in the pathogenesis of the diseases, provide promising alternatives (14). Studies need to uniform and improve a treatment strategy for the autoimmune bullous dermatoses, which is considered to be a new approach that targets the dysfunction of the immune system, instead of widespread immunosuppression, such as anti-CD 20 anti-bodies, such as rituximab. Up to date, in Europe and the United States, a first-line therapy for moderate and severe pemphigus vulgaris is approved and already highlighted in the 2020, 2022, and 2023 in the guidelines of the European Academy of Dermatology and Venereology (EADV) (15-17).

Najzahvaćenija područja u usnoj šupljini su nepce, labijalna sluznica, bukalna sluznica, jezik i gingiva, ali mogu biti zahvaćena i njezina druga područja (3, 4). Pemfigoid, uključujući bulozni pemfigoid, cikatricijalni pemfigoid i gestacijski pemfigoid, manifestira se supepitelnim mjehurićima i naslagama IgG-a. Istaknimo, bulozni pemfigoid uglavnom pogađa starije osobe (starije od 60 godina), no vrlo je rijedak kod djece i zato nema predispoziciju za etničke skupine ili različite biološke spolove (1). Klinički ga karakterizira kombinacija eritematoznih makula, papula i buloznih erupcija koje svrbe. Lezije su uglavnom raširene, obično simetrične i mogu zahvatiti različita područja kože poput vanjskih dijelova udova, trbuha, glave i vrata, a rjeđe sluznice i oralnu sluznicu (1 – 5).

Klasična terapija pemfigusa vulgarisa, sa svrhom liječenja bolesti, uključuje sistemsku primjenu kortikosteroida. Ako se ne liječi ili se neodgovarajuće liječi, stanje može biti kobno zbog gubitka funkcije epidermalne barijere na velikom području kože (3, 4, 6).

Liječenje pemfigusa vulgarisa i pemfigoidnih bolesti često može biti izazovno. Danas postoje preporuke i univerzalne smjernice za liječenje, ali nedostaje standardni terapijski protokol. Posljedično, terapijske pristupe obično određuju kliničari tako da uzimaju u obzir kliničku anamnezu, dob, težinu bolesti, anatomsku distribuciju lezija, terapijski odgovor i nuspojave kod pacijenata (7, 8). Kako bi se razumjelo zahtijeva li liječenje imunosupresivnu sistemsku terapiju ili konzervativni pristup, ključna je točna i rana dijagnoza autoimunih buloznih bolesti, s obzirom na to da su kortikosteroidi obično prva linija liječenja (9, 10). Napredak u liječenju buloznih autoimunih bolesti uveo je ciljane terapijske strategije, uključujući monoklonska antitijela protiv CD20, inhibitore Brutonove tirozin kinaze (BTK), inhibitore FcRn-a (blokatore Fc receptora novorođenčadi) i terapiju himernim receptorom autoantitijela (CAAR) i T-stanicama za pemfigus vulgaris. Svrha tih novih pristupa jest modulirati imunosni odgovor, posebno da bi se ponudilo više potencijalnih koristi od tradicionalnih vrsta terapije (11 – 13). S druge strane, za bulozni pemfigoid trenutačno se istražuju biološki agensi poput dupilumaba (antagonist IL-4Rα), omalizumaba (monoklonsko antitijelo protiv IgE-a) i terapije usmjerene na IL-5/eozinofile. Specifični putevi djelovanja terapija uključenih u patogenezu bolesti pružaju obećavajuće alternative (14). Istraživanja trebaju ujednačiti i poboljšati strategiju liječenja autoimunih buloznih dermatoza, što se smatra novim pristupom koji cilja na disfunkciju imunosnog sustava, umjesto na široko rasprostranjene imunosupresije, poput anti-CD20 antitijela i rituksimaba. Do danas je u Europi i Sjedinjenim Američkim Državama odobrena terapija prve linije za umjereni i teški pemfigus vulgaris i već je istaknuta u smjernicama Europske akademije za dermatologiju i venerologiju (EADV) za 2020., 2022. i 2023. godinu (15 – 17). Svrha ovog istraživanja bila je procijeniti epidemiološke i terapijske aspekte pemfigusa vulgarisa i pemfigoida, s naglaskom na preporuke za liječenje, uključujući rituksimab i kortikosteroide u specifičnoj bolničkoj populaciji unutar 10-godišnje opservacijske studije.

This study aimed to evaluate the epidemiological and therapeutic aspects of pemphigus vulgaris and pemphigoid, focusing on treatment recommendations, including rituximab and corticosteroids in a specific hospital population, in a 10 year observational study.

Objectives

The aim of this study was to assess the epidemiological characteristics, therapeutic treatments, and remission intervals of pemphigus vulgaris and pemphigoid in a hospital population.

Materials and methods

Experimental design

This retrospective study was performed at a single institution, throughout a period of 10 years at the Dermatology Service of the Hospital de Santa Maria (Santa Maria Local Health Unit, ULS Santa Maria) in Lisbon, Portugal. The collection of data was accomplished through medical records of the patients treated in this hospital. The research was performed following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines (18). Ethical approvals were achieved by the Ethics Committee of the Lisbon Academic Medical Center (CAML) with the registration numbers 30/23 and 19/23 for both pathology groups, namely Pemphigus and Pemphigoid, and it was approved on March 3, 2023.

Sample

The sample consisted of the patients with histopathological diagnoses of pemphigus vulgaris or pemphigoid between the years of 2013 and 2022 from Cutaneous Histopathology Laboratory (LHC) of the Dermatology Service of ULS Santa Maria. All data used for this research purposes, including demographic, clinical, and treatment data of the patients were collected anonymously from medical records using the database with exclusive purpose for study research. The data remain confidential throughout the whole process, in accordance with the Law No. 58/2019, of August 8 (19).

Statistical Analysis

For analyzing the data, we used IBM SPSS® (Statistical Package for the Social Sciences) version 29, with Clopper-Pearson 95% confidence intervals (CI) for proportions.

Results

Pemphigus vulgaris

Demographics: The total number of the patients was 99 (49 females, 50 males) with a range age between 51 and 80 years**.**

Clinical Manifestation, Treatment and Outcomes: The overall percentage of the manifestation in patients was as follows: 56.6% with cutaneous lesions, 13.1% with mucosal lesions, and 30.3% with mucocutaneous involvement. Oral lesions were mainly in the buccal mucosa (52.5%) and lips (50%), (Figure 1). Corticosteroids were prescribed in 79 cas-

Ciljevi istraživanja

Cilj ovog istraživanja bio je procijeniti epidemiološke karakteristike, terapijske opcije i intervale remisije pemfigusaa vulgaris i pemfigoida u hospitaliziranoj populaciji.

Materijali i metode

Eksperimentalni dizajn

Ovo retrospektivno istraživanje provedeno je u jednoj ustanovi tijekom 10 godina u Dermatološkoj službi/ambulanti bolnice Santa Maria (lokalna zdravstvena jedinica Santa Maria, ULS Santa Maria) u Lisabonu (Portugal). Podatci su prikupljeni iz medicinskih kartona pacijenata liječenih u toj zdravstvenoj ustanovi. Istraživanje je obavljeno prema smjernicama za izvještavanje STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) (18). Etičko odobrenje za obje patološke skupine – pemfigus i pemfigoid – dalo je 3. ožujka 2023. Etičko povjerenstvo Akademskog medicinskog centra u Lisabonu (CAML) s registracijskim brojevima 30/23 i 19/23,.

Uzorak

Uzorak se sastojao od pacijenata s patohistološkim dijagnozama pemfigusa vulgarisa ili pemfigoida između 2013. i 2022. godine iz Laboratorija za kožnu patohistologiju (LHC) Dermatološke službe/ambulante Sveučilišta San Francisco u Santa Mariji. Svi podatci korišteni u ovom istraživanju, uključujući demografske, kliničke i one o liječenju pacijenata, prikupljeni su anonimno iz medicinske dokumentacije upisane u bazu podataka isključivo za studijsko istraživanje. Podatci su ostali povjerljivi tijekom cijelog procesa, u skladu sa Zakonom br. 58/2019. od 8. kolovoza (19).

Statistička analiza

Za analizu podataka korišten je IBM SPSS® (Statistical Package for the Social Sciences) verzija 29, s Clopper-Pearsonovim 95-postotnim intervalima pouzdanosti (CI) za proporcije.

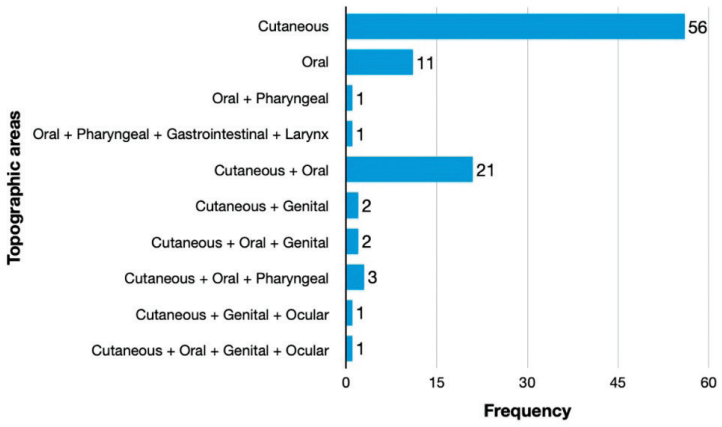
Rezultati

Pemfigus vulgaris

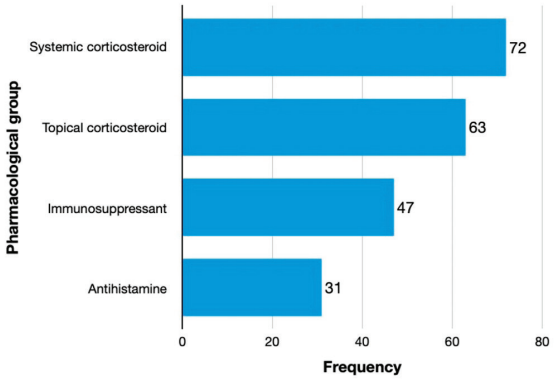
Demografija: Ukupan broj pacijenata bio je 99 (49 žena, 50 muškaraca) u dobi između 51 i 80 godina.

Klinička manifestacija, liječenje i ishodi: Ukupni postotak manifestacija kod pacijenata bio je sljedeći: 56,6 % s kožnim lezijama, 13,1 % s mukoznim lezijama i 30,3 % s mukokutanim zahvaćanjem. Lokalizacija oralnih lezija bila je uglavnom na bukalnoj sluznici (52,5 %) i usnama (50 %) (slika 1.). Kortikosteroidi su propisani u 79 slučajeva (63,4 %), najčešće prednizolon (84,8 %) (slika 2.). Vjerojatnost da će pacijent

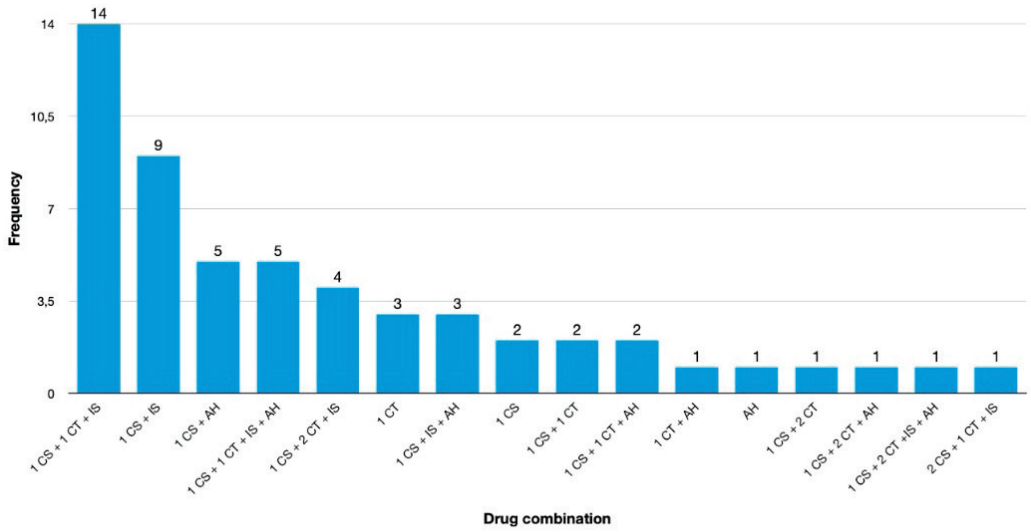
1.



2.



3.



CT – Topical corticosteroid; CS – Systemic corticosteroid; IS – Immunosuppressant; AH – Antihistamine

4.

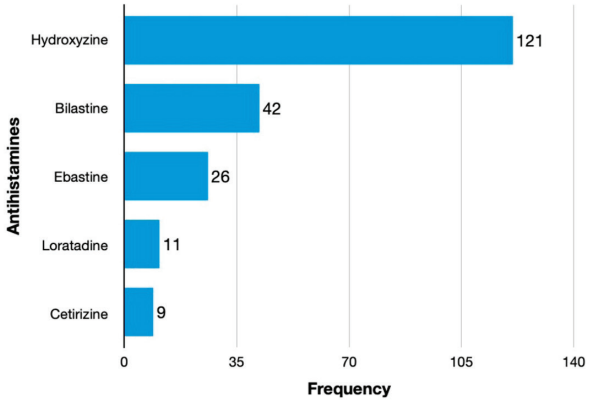


Figure 1 Topographic distribution of the first appearance of pemphigus vulgaris
Slika 1 Topografska distribucija prve pojave pemfigus vulgaris
Figure 2 Prescribed pharmacological groups
Slika 2 Propisane farmakološke skupine
Figure 3 Drug combinations used in the initial therapeutic regimen
Slika 3 Kombinacije lijekova korištene u početnom terapijskom režimu
Figure 4 Prescribed antihistamines
Slika 4 Propisani antihistaminici

es (63.4%), prednisolone being the most common one prescribed (84.8%), (Figure 2). The probability of an individual being medicated with prednisolone varies between 40.9% and 58.4%, betamethasone between 16.2% and 31.0%, clobetasol propionate from 6.9% to 18.5%, and hydrocortisone between 4.1% to 14.1% (95% CI). Given the CI presented, it was observed that there were significant differences between the prescription of prednisolone and the other active ingredients. The most common dose of prednisolone used was 20 mg (n=65) being the route of administration exclusively systemic. Out of 79 individuals who underwent systemic corticosteroid therapy, 59 (74.7%) of them were reported being tapered. However, the therapeutic regimen for weaning was different for every individual that was included in this study. Additionally, azathioprine was the most prescribed immunosuppressant (59,6%), whereas antihistamines were used in 31 patients (31.3%), the most used one was hydroxyzine (54.8%). The probability of the active ingredient used to be hydroxyzine ranged from 36.0% to 72.7%. For ebastine, the values ranged from 7.5% to 37.5%, bilastine between 3.6% and 29.8% (95% CI), and rituximab was used in 21 patients (21.2%). On the other hand, intravenous immunoglobulin cycles were a therapeutic option for 16 patients (16.2%), from which 6 underwent both therapies. Mean remission time was 304 days, with 35.4% of patients experiencing relapse. The first-line use of therapeutic regimen by patients was the same at the time of complete remission (Figure 3).

Pemphigoid

Demographics: The total number of the patients was 227 (108 females, 119 males) with a mean age of 70-89 years.

Clinical Manifestations, Treatment and Outcomes: 98.2% of patients had skin lesions, with 6.2% of them presenting oral lesions (Table 1). Prednisolone (90.5%) and clobetasol propionate (66.0%) were the most prescribed treatments. The most relevant dose associated was 20 mg for prednisolone (90.1%) and 0.5 mg/g (99.2%) for clobetasol propionate. Most of the individuals who underwent systemic corticosteroid therapy reported that they had been weaned (84.4%), but the regimen applied varied considerably. Hydroxyzine was the most prescribed antihistamine (57.9%), (Figure 4). Azathioprine was the most common immunosuppressant (76.8%), followed by methotrexate (15.9%). In the group of antibiotics, the most prescribed one was doxycycline (42.3%). Overall, the probability of prednisolone being prescribed is between 18.1% and 23.6%, clobetasol propionate between 12.8% and 17.7%, hydroxyzine between 11.6% and 16.3%, and doxycycline between 5.1% and 8.5% (95% CI). Statistically, a significant relationship between the prescription of prednisolone and other drugs was observed (Table 2). Mean cure time was 148 days, with 28.7% of patients experiencing relapse.

Discussion

This study found no significant predilection for pemphigus vulgaris among biological sexes, with 49 females and 50 males diagnosed, which is consistent with findings in the literature (20-22). However, most retrospective studies suggest

biti liječen prednizolonom varira između 40,9 % i 58,4 %, betametazonom između 16,2 % i 31,0 %, klobetazol propionatom od 6,9 % do 18,5 % i hidrokortizonom između 4,1 % i 14,1 % (95 % CI). S obzirom na prikazani CI, uočavaju se značajne razlike između propisivanja prednizolona i ostalih aktivnih sastojaka. Najčešće korištena doza prednizolona bila je 20 mg (n = 65), a put primjene bio je isključivo sistemski. Od 79 pacijenata podvrgnutih sistemskoj kortikosteroidnoj terapiji, njih 59 (74,7 %) izvijestilo je o postupnom smanjenju doze. No terapijski režim za ukidanje doze bio je drukčiji za svakog pacijenta uključenog u ovo istraživanje. Uz to, azatioprin je bio najčešće ordinirani imunosupresiv (59,6 %), antihistaminike je dobio 31 pacijent (31,3 %), a najčešće je primijenjen hidroksizin (54,8 %). Vjerojatnost da je aktivni sastojak bio hidroksizin iznosila je od 36,0 % do 72,7 %, za ebastin su se vrijednosti kretale od 7,5 % do 37,5 %, za bilastin između 3,6 % i 29,8 % (95 % CI), a rituksimab je propisan 21 pacijentu (21,2 %). S druge strane, intravenski ciklusi imunoglobulina bili su terapijska opcija za 16 pacijenata (16,2 %), od kojih je 6 podvrgnuto objema terapijama. Prosječno vrijeme remisije bilo je 304 dana, s time da je 35,4 % pacijenata doživjelo recidiv. Pacijenti su primjenjivali jednak terapijski režim tijekom potpune remisije (slika 3.).

Pemfigoid

Demografija: Ukupan broj pacijenata bio je 227 (108 žena, 119 muškaraca), a njihova prosječna dob bila je od 70 do 89 godina.

Klinička manifestacija, liječenje i ishodi: Ukupno je 98,2 % pacijenata imalo kožne lezije, a 6,2 % oralne (tablica 1.). Prednizolon (90,5 %) i klobetazol propionat (66,0 %) bili su najčešće propisivani lijekovi. Najrelevantnija doza bila je 20 mg za prednizolon (90,1 %) i 0,5 mg/g (99,2 %) za klobetazol propionat. Većina pacijentica podvrgnutih sistemskoj kortikosteroidnoj terapiji izvijestila je da su prestale s dojenjem (84,4 %), ali primijenjeni režim znatno je varirao. Hidroksizin je bio najčešće propisivani antihistaminik (57,9 %) (slika 4.). Najčešći imunosupresiv bio je azatriopin (76,8 %), a slijedio ga je metotreksat (15,9 %). U skupini antibiotika najčešće je bio propisivan doksiciklin (42,3 %). Sveukupno, vjerojatnost propisivanja prednizolona je između 18,1 % i 23,6 %, klobetasol propionata između 12,8 % i 17,7 %, hidroksizina između 11,6 % i 16,3 %, a doksiciklina između 5,1 % i 8,5 % (95 % CI). Statistički je uočena značajna povezanost između propisivanja prednizolona i drugih lijekova (tablica 2.). Prosječno vrijeme izlječenja bilo je 148 dana, a 28,7 % pacijenata doživjelo je recidiv.

Rasprava

Autori ovog istraživanja nisu pronašli značajnu predilekciju pemfigusa vulgarisa među biološkim spolovima, s dijagnozom 49 žena i 50 muškaraca, što je u skladu s nalazima iz literature (20 – 22). No u većini retrospektivnih istraživa-

Table 1. Topographic distribution of appearance by pemphigoid subtype
Tablica 1. Topografska distribucija prema podtipu pemfigoida

	Pemphigoid	Bullous pemphigoid	Gestational pemphigoid	Cicatricial pemphigoid	Total
Cutaneous	3	198	5	1	207
Oral	0	0	0	2	2
Ocular	1	0	0	0	1
Cutaneous + Oral	0	7	1	0	8
Cutaneous + Oral + Genital	0	1	0	0	1
Cutaneous + Genital	0	5	0	0	5
Cutaneous + Oral + Nasal	0	1	0	0	1
Cutaneous + Oral + Nasal + Gastointerstinal	0	1	0	0	1
Oral + Ocular	0	0	0	1	1
Total	4	213	6	4	227

Table 2. Confidence intervals for the prescribed drugs
Tablica 2. Intervali pouzdanosti za propisane lijekove

	Lower limit	Upper limit
Prednisolone	18,1%	23,6%
Clobetasol propionate	12,8%	17,7%
Hydroxyzine	11,6%	16,3%
Doxycycline	5,1%	8,5%
Azathioprine	4,6%	7,9%
Fusidic Acid	4,0%	7,1%
Betamethasone	3,7%	6,7%
Bilastine	3,5%	6,4%
Ebastina	2,9%	4,3%
95 % Confidence intervals		

a higher prevalence in females, possibly due to greater health-seeking behavior (6, 23–28). Similarly, bullous pemphigoid showed no difference between biological sexes (102 females, 111 males; p=0.584), although some studies report female predominance (29–31).

Contrary to the literature suggesting that the primary initial manifestation of pemphigus vulgaris is oral mucosa, this study found that cutaneous and mucocutaneous lesions were more prevalent (86.9%). Mucocutaneous involvement was observed in 30.3% of cases, while exclusively mucosal manifestations occurred in 13.1%, aligning with studies by Cura et al. (21.9%) and Baican et al. (13.9%) (6, 24, 25, 32). Among pemphigus vulgaris patients, 40.4% of them had oral lesions, most commonly in the buccal mucosa (52.2%) and lips (50%). In bullous pemphigoid, mucosal involvement was rare (4.2% oral lesions), lower than the 10–20% reported in some studies (8, 33-35).

Corticosteroids, often combined with immunosuppressants were the primary treatment for pemphigus vulgaris, which is consistent with the literature (2, 6, 25, 26, 33, 36). Rituximab, approved in 2018 for moderate to severe pemphigus vulgaris, was used in 21.2% of patients, thus demonstrating high efficacy and safety (3, 5, 13, 33, 37). Notably, it induced remission in a 10-year-old child within two months. Intravenous immunoglobulin (IVIG) was used as an adjuvant in severe or refractory cases, with studies showing its potential to reduce corticosteroid dependence (38, 39). Emerg-

nja sugerira se veća prevalencija kod žena, možda zbog veće skrbi o zdravlju (6, 23 – 28). Slično tomu, bulozni pemfigoid nije pokazao razliku između bioloških spolova (102 žene, 111 muškaraca; p = 0,584), iako se u nekim studijama izvještava o ženskoj predominaciji (29 – 31).

Suprotno podatcima iz literature koji sugeriraju da je početna manifestacija pemfigusa vulgarisa oralna sluznica, autori ovog istraživanja otkrili su da su kožne i mukokutane lezije bile češće (86,9 %). Mukokutana zahvaćenost uočena je u 30,3 % slučajeva, a isključivo mukozne manifestacije pojavile su se u 13,1 %, što je u skladu s istraživanjima Cure i suradnika (21,9 %) i Baicana i suradnika (13,9 %) (6, 24, 25, 32). Među pacijentima s pemfigusom vulgarisom njih 40,4 % imalo je oralne lezije, najčešće na bukalnoj sluznici (52,2 %) i usnama (50 %). Kod buloznog pemfigoida zahvaćenost sluznice bila je rijetka (4,2 % oralnih lezija), niža od 10 do 20 % koliko je zabilježeno u nekim studijama (8, 33 – 35).

Kortikosteroidi, često u kombinaciji s imunosupresivima, bili su primarni tretman za pemfigus vulgaris, što je u skladu s literaturom (2, 6, 25, 26, 33, 36). Rituksimab, odobren 2018. za umjereni do teški pemfigus vulgaris, primijenjen je kod 21,2 % pacijenata i pokazao je visoku učinkovitost i sigurnost (3, 5, 13, 33, 37). Značajno je da je izazvao remisiju kod 10-godišnjeg djeteta unutar dva mjeseca. Intravenski imunoglobulin (IVIG) korišten je kao adjuvant u teškim ili refraktornim slučajevima, a u istraživanjima se ističe njegov potencijal za smanjenje ovisnosti o kortikosteroidima

ing research highlights biomarkers such as TNF-α and anti-Dsg antibodies as promising tools for diagnosis and monitoring, although this study did not explore them (40).

For bullous pemphigoid, corticosteroids remained the first-line treatment, with prednisolone (90.5%) and clobetasol propionate (66.0%) being the most prescribed medications. While systemic corticosteroids have been standard for a long period of time, recent evidence supports the superiority of potent topical corticosteroids such as clobetasol propionate control and reduced side effects (38–40). Antihistamines were the second most prescribed group, primarily for pruritus, although the literature is limited when it comes to their usage. Immunosuppressants and antibiotics, such as doxycycline, were also widely used, particularly in cases where corticosteroids were contraindicated (41, 44–48).

Treatment decisions for pemphigus vulgaris and bullous pemphigoid remain individualized, influenced by factors such as disease severity, patient comorbidities, and clinician experience (5, 26, 27, 46-48).

This study highlights the predominance of corticosteroids in treating pemphigus vulgaris and pemphigoid, which is consistent with the current literature. Rituximab, approved for pemphigus vulgaris in 2018, has shown efficacy as an alternative treatment. For pemphigoid, prednisolone and clobetasol propionate remain the primary treatments, with emerging evidence supporting the use of topical corticosteroids over systemic options.

Since these epidemiological studies are retrospective from the collection of clinical information from one unique hospital, ULS Santa Maria, the results cannot be extrapolated to the general population.

Conclusions

First-line treatments for conditions such as pemphigus include the use of systemic prednisolone and topical betamethasone as corticosteroids, while azathioprine is the most common non-steroid immunosuppressive therapy. Hydroxyzine is the first-line antihistamine, and rituximab is reserved for refractory cases. It is administered to approximately 25% of patients. In the case of pemphigoid, prednisolone is the most prescribed systemic corticosteroid, and clobetasol propionate is the preferred topical option. These approaches highlight the importance of combined and individualized therapies for the effective management of these conditions.

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(38, 39). Autori novih istraživanja ističu biomarkere poput TNF-α i anti-Dsg antitijela kao obećavajuće za dijagnozu i praćenje, iako ih se u ovoj studiji nije istraživalo (40).

Za bulozni pemfigoid kortikosteroidi su ostali terapija prve linije, s prednizolonom (90,5 %) i klobetasol propionatom (66,0 %) koji su se najčešće propisivali. Dok su sistemski kortikosteroidi dugo bili standard, nedavni dokazi podupiru superiornost potentnih lokalnih kortikosteroida, poput klobetasol propionata, u kontroli i smanjenju nuspojava (38 – 40). Antihistaminici su bili druga najčešće propisivana skupina, uglavnom za svrbež, iako je literatura ograničena kada je u pitanju njihova upotreba. Imunosupresivi i antibiotici, poput doksiciklina, također su se često primjenjivali, posebno kada su kortikosteroidi bili kontraindicirani (41, 44 – 48).

Odluke o liječenju pemfigusa vulgarisa i buloznog pemfigoida ostaju individualne, pod utjecajem čimbenika kao što su težina bolesti, komorbiditeti pacijenta i iskustvo kliničara (5, 26, 27, 46 – 48).

U ovom istraživanju ističe se prevladavanje kortikosteroida u liječenju pemfigusa vulgarisa i pemfigoida, što je u skladu s aktualnom literaturom. Rituksimab, odobren za pemfigus vulgaris 2018. godine, pokazao je učinkovitost kao alternativna terapija. Za pemfigoid primarna terapija je i dalje prednizolon i klobetasol propionat, s novim dokazima koji podupiru upotrebu lokalnih kortikosteroida u usporedbi sa sistemskim opcijama.

Budući da su ove epidemiološke studije retrospektivne na temelju prikupljanja kliničkih podataka iz jedne jedinstvene bolnice, ULS Santa Maria, rezultati se ne mogu primijeniti na opću populaciju.

Zaključci

Liječenje prve linije za stanja poput pemfigusa uključuje upotrebu sistemskog prednizolona i lokalnoga betametazona kao kortikosteroida, a azatioprin je najčešća nesteroidna imunosupresivna terapija. Hidroksizin je antihistaminik prve linije, a rituksimab se propisuje za refraktorne slučajeve i primjenjuje se kod otprilike 25 % pacijenata. U slučaju pemfigoida, prednizolon je najčešće propisivani sistemski kortikosteroid, a klobetazol propionat preferirana je lokalna opcija. U tim pristupima ističe se važnost kombiniranih i individualiziranih terapija za učinkovito liječenje ovih stanja.

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Author's contribution: The authors conform contribution to the paper as follows: **C. P. P.** - Study Conception and Design; **L. F., M. M. and A. R. D. A.** - Data Collection; **R. S., C. P. P., P. F.** - Analysis and Interpretation of results; **C. P. P., A. R. D. A.** Draft Manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

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Sažetak

Svrha rada: Cilj ovog istraživanja bio je procijeniti epidemiološke podatke o pemfigus vulgaris i pemfigoid, s posebnim naglaskom na karakteristike, kliničke manifestacije i pristupe liječenju. **Materijali i metode:** Istraživanje je obuhvaćalo pacijente kojima je dijagnosticiran pemfigus vulgaris ili pemfigoid u dermatološkoj službi/ambulanti lokalne zdravstvene jedinice Santa Maria između 2013. i 2022. godine. Za analizu je korišten statistički softver IBM SPSS® verzija 29, s Clopper-Pearsonovim 95-postotnim intervalima pouzdanosti (CI). **Rezultati:** Ukupan broj pacijenata uključenih u ovo istraživanje bio je 99 s pemfigusom vulgarisom (49 žena, 50 muškaraca) i 227 s pemfigoidom (108 žena, 119 muškaraca). Pacijentima liječenima od pemfigusa vulgarisa najčešće propisivani lijekovi bili su kortikosteroidi, a slijede imunosupresivi. Dodatno je rituksimab ordiniran 21 pacijentu. Interval bolesti bio je 304 dana, s intervalom bez simptoma od 415 dana za pacijente s relapsom. Za pemfigoid primarno se liječenje sastojalo od primjene kortikosteroida koji su bili glavna terapija, a u mnogim slučajevima kombinirani su s drugim lijekovima kao što su antihistaminici, antibiotici i imunosupresivi. Prosječno vrijeme izlječenja bilo je 148 dana, pri čemu je 32,0 % pacijenata tvrdilo da su doživjeli relaps. **Zaključak:** Zaključno, uočeno je da kortikosteroidi, posebno prednizolon, ostaju najvažnija farmakološka terapija za pemfigus vulgaris i pemfigoid. Međutim, rituksimab je učinkovita farmakološka alternativa za pemfigus, a klobetazol propionat postaje sve popularniji i sve je češće jedan od preferiranih lijekova za pemfigoid.

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