SKIN

IN-DEPTH REVIEW

Treatment of Pyodermatitis-Pyostomatitis Vegetans: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Pyodermatitis-pyostomatitis vegetans (PDV-PSV) is a rare muco-cutaneous disorder characterized by vegetating and pustular plaques and is often associated with inflammatory bowel disease (IBD). The purpose of this study was to systematically identify and analyze reports of PDV-PSV to determine the most effective treatment.

Methods: Reports of PDV-PSV were identified using the OVID-Medline database from inception through November 2019. Publications were excluded if no new patient case was included, if there was not clinical and histological evidence of PDV, PSV, or PDV-PSV, or if no treatment was discussed.

Results: The final sample was comprised of 74 publications plus an additional patient from the authors' institution, corresponding to 95 total patients. The basis of the review and analysis is limited to case reports and case series, which likely only report the cases with positive outcomes. Statistical analysis revealed that oral corticosteroids (OCS), 6-mercaptopurine/azathioprine, oral calcineurin inhibitors (OCNI), 5-aminosalicylic-acid (5-ASA), and biologics (BIO) were the most effective treatments for PDV-PSV. Topical medications, colchicine, oral dapsone, and other antibiotics were ineffective treatments, with topical medications being the least effective option. When OCS are used, they work best when used as initial treatment to induce remission. 5-ASA and BIO are most effective when used as maintenance therapies after initial remission.

Conclusions: Thus, first line therapy for PDV-PSV should begin with OCS with transition to steroid-sparing agents including OCNI, BIO, and 5-ASA if indicated.

INTRODUCTION

Pyodermatitis-pyostomatitis vegetans is a rare mucocutaneous disorder often associated with inflammatory bowel disease (IBD) that can be extremely difficult to treat. Due to is rarity, no standardized trials exist comparing the efficacy of different medications, and recommendations for treatment of this disease are limited and not evidence-based.

Pyodermatitis vegetans (PDV) was first described by the French dermatologist Francois Hallopeau in 1898 as a distinct disease of vegetating plaques of the skin which he termed "pyodermite vegetante."[1] In 1949, McCarthy described three cases of PDV with mucosal-dominant disease as "pyostomatitis vegetans."[2] Clinically, PDV is

characterized by erythematous pustules that become exudative vegetative plaques with well-defined elevated borders.[3] Pyostomatitis-vegetans (PSV) similarly presents with sterile pustules on mucosal sites which erode and coalesce into "snail track" ulcers.[4] Histological analysis of these lesions reveals eosinophilic or neutrophilic microabscesses and infiltrates, epidermal hyperplasia and often focal acantholysis.[1,3,5] The spectrum of disease is referred to as pyodermatitis-pyostomatitis vegetans (PDV-PSV), with patients presenting with cutaneous symptoms only, mucosal symptoms only, or both cutaneous and mucosal symptoms. Since 1949, PDV-PSV has been documented in association with IBD in 80% of cases.[1,5,6] Treatment is often directed at underlying IBD, though cutaneous and mucosal disease can prove refractory.

The purpose of this review was to determine the most effective treatment options for PDV-PSV based on the success of medications used for patients with PDV-PSV found in the literature. The demographics of this population are presented, as well as the medications attempted for treatment. Medications are compared to determine which are most effective for the treatment of PDV-PSV.

METHODS

Search strategy and Inclusion Criteria

A systematic review was conducted up to November 2019, using the search terms "pyostomatitis vegetans" and "pyodermatitis vegetans" in the PubMed/Medline database. All reports were analyzed by two independent reviewers to determine which met inclusion criteria. Review papers were used to find any reports missed in the initial literature search. Reports were included in the review if there was a new patient case, clinical and histological evidence of PDV, PSV, or PDV-PSV, and treatment was discussed. A diagnosis of PDV-PSV was confirmed by one dermatologist based on the clinical and histological description of PDV-PSV in each report. The exclusion criteria included any report that did not meet the above criteria, which included all review papers, reports without evidence of PDV-PSV, or those with cases that did not discuss treatment options. An additional case from the authors' institution was also included for meta-analysis.

Data Extraction and Preparation

Using the PRISMA guidelines for extracting and assessing data, data from each paper was collected by two independent reviewers and is summarized in Table 1, along with the ratings of the quality of evidence of each paper. No methods were used to assess the risk of bias, as this review and analysis consists only of case reports and case series. Data collected included patient demographics, including sex, age, and ethnicity, presence and type of concomitant inflammatory bowel disease, histological description of PDV-PSV (including immunofluorescence results), complete blood count results prior to initiating treatment (including presence of eosinophilia), inflammatory markers (Erythrocyte Sedimentation Rate (ESR) or C-reactive Protein (CRP)) prior to initiating treatment, and all medications attempted with associated response.

Treatment responses were separated into three categories depending on the type of response: partial response, complete response, and no response. Partial response was defined as incomplete resolution of lesions, with the disease described as: "relapsing intermittently," "having slight clinical improvement,"

Table 1. Summary of findings in 95 reported cases

Report	Rating of QoE	Demographic	IBD	PDV/ PSV	Response to Treatment				
					No Response	Partial Response	CR-I	CR-M	CR-D
Abellaneda 2011[7]	5	35M, Spanish	UC	PDV-PSV	AZA, MTX, DAP, COL, RET, 5-ASA, MSC		OCS	AZA + 5-ASA	
Ahn 2004[8]	5	33F, Korean	UC	PDV-PSV		DAP, COL, OSC	DAP, COL, OSC	5-ASA	
Al-Rimawi 1998[9]	5	7M	UC	PSV	OCS, 5-ASA, CHL				
		5F	Chronic colitis	PSV	T-CS/CNI, OCS				
Atarbashi-Moghadam 2016[10]	5	39F	CD	PSV				5-ASA, AZA	
Ayangco 2002[11]	5	22F, White	CD	PSV		T-CS/CNI		5-ASA	
Ballo 1989[12]	5	39F	UC	PSV	ABX, T-CS/CNI, MSC		OCS	5-ASA	
Bens 2003[13]	5	35F	CD	PSV			BIO	MTX	
Bertlich 2019[14]	5	51F	UC	PDV-PSV	AZA + OCS + T-CS/CNI			BIO, OCS, T-CS/CNI	
Bianchi 2001[4]	5	48F	UC	PDV			ABX	5-ASA	
Brinkmeier 2001[15]	5	32F, White	None	PDV-PSV	DAP, 5-ASA			OCS, T-CS/CNI, OCS + RET, OCS + OCNI	
Calobrisi 1995[16]	5	65M, White	UC	PSV				T-CS/CNI	total colectomy
Canpolat 2011[17]	5	64M	UC	PDV			OCS, ABX	5-ASA	
Carvalho 2016[18]	5	79F	None	PDV					ABX + OCS
Cataldo 1981[19]	5	48M, White	CD	PSV		T-CS/CNI			OCS
Chan 1991[20]	5	23M, White	UC	PSV			FES, T-CS/CNI, OCS, ABX	5-ASA	
		17F, White	UC	PSV			5-ASA, T-CS/CNI, FES		
Chaudhry 1999[21]	5	63M	UC	PSV					T-CS/CNI, ABX
Clark 2016[3]	4	22F	UC	PSV				5-ASA, T-CS/CNI	
		30M	UC	PDV-PSV	OCS, DAP, AZA, NYS, PTR				
		29M	CD	PSV	OCS, DAP				

		54M	CD	PSV	OCS, T-CS/CNI, DAP, OCNI, MM			BIO	
		44F	UC	PDV-PSV				OCS, T-CS/CNI, PTR	
		21M	UC	PDV-PSV				DAP, T-CS/CNI	
		58M	CD	PDV-PSV	OCS, T-CS/CNI, DAP, MSC				
Dodd 2017[22]	5	30F	CD	PDV-PSV	BIO, AZA	OCS, T-CS/CNI		BIO + DAP	
Dupuis 2016[23]	5	48M	Colitis	PDV-PSV			OCS		
Ficarra 1993[24]	5	45F, Italian	CD	PDV-PSV		Zinc			OCS
Forman 1965[25]	5	45F	UC	PDV-PSV					ACTH, ABX
		44F	UC	PDV-PSV		DAP	DAP	ABX, T-CS/CNI	
Gonzalez-Moles 2008[26]	5	84F	None	PSV					T-CS/CNI + NYS
Hansen 1983[27]	5	37M, White	UC	PSV			OCS	OCS + 5-ASA	
Harish 2006[28]	5	35M	UC	PDV			OCS	5-ASA	
Healy 1994[29]	5	27M, White	UC	PSV			DAP, OCS, T-CS/CNI, AZA	5-ASA	
		24F, White	None	PSV				CHL	
Kajihara 2013[30]	5	78M	None	PDV			OCS + T-CS/CNI + COL	OCS + COL	
Kalman 2013[31]	5	41F	CD	PSV			OCS	BIO	
Khader 2016[32]	5	21M	UC	PDV					OCS
Kim 2015[33]	5	27M	CD	PDV-PSV			COL; OSC, DAP (high dose)	OCS, DAP (low dose)	
Kitayama 2010[34]	5	51F, Japanese	UC	PDV-PSV			OCNI, OCS, AZA	5-ASA	
Knapp 2016[35]	5	10M	UC	PSV	ABX	AZA	OCS		T-CS/CNI + AZA
Ko 2009[36]	5	47M	None	PDV-PSV	ABX, T-CS/CNI		OCS (high dose)	OCS (low dose)	
		24F	None	PDV-PSV			OCS	OCS	
Konstantopoulou 2005[37]	5	19M	UC	PDV-PSV	ABX, T-CS/CNI	DAP		OCS + ABX	
Leibovitch 2005[38]	5	29M	UC	PDV-PSV	ABX		OCS, T-CS/CNI	5-ASA, OCS	

Li 2018[39]	5	25M	None	PDV-PSV			OCS	5-ASA	
Lopez 2012[40]	5	35M	UC	PDV-PSV	MSC			T-CS/CNI, NYS, 5-ASA	
Lourenco 2010[41]	5	63F	UC	PSV				OCS, DAP	
Maseda 2017[42]	5	49M	CD	PDV					ABX
Markiewicz 2007[43]	5	30M, White	UC	PSV				5-ASA	
Marks 1962[44]	5	20M	UC	PDV-PSV	ABX, DAP	ABX		OCS, ACTH	
Matias 2011[45]	5	47F	None	PDV	ABX	OCS (low dose) + DAP	OCS (higher dose)		
McCarthy 1963[2]	5	27M, White	UC	PSV				T-CS/CNI	
Mehravaran 1997[5]	5	43F	None	PDV-PSV			OCS+AZA	OCS	
Merkourea 2013[46]	5	58M	CD	PSV	5-ASA (“low dose”)				
Mesquita 2012[47]	5	12M	None	PDV-PSV			OCS + AZA	DAP	
Mijandrusic-Sincic 2010[48]	5	23F	CD	PSV				BIO	
		32F	UC	PSV					AZA
Mizukami 2019[49]	5	29F	UC	PSV	OCS				DAP
Molnar 2011[50]	5	16M	CD	PSV					OCS, AZA+BIO
Moloney 2011[51]	5	50F	UC	PDV-PSV		DAP		DAP + AZA + 5-ASA	
Naish 1970[52]	5	26M, Black	UC	PSV				OCS	
Nayak 2017[53]	5	33F	UC	PDV-PSV		OCS			OCS
Neville 1985[54]	5	47F, Black	CD	PSV			OCS	5-ASA + OCS	
Nico 2012[55]	4	63F	UC	PSV			OCS	OCS	
		33M	Colitis	PSV			OCS	T-CS/CNI	
		33F	UC	PSV					OCS
		34M	UC	PSV					OCS
Niezgoda 2018[56]	5	69M	UC	PSV				OCS + OCNI	
Nigen 2003[57]	5	22F	None	PDV-PSV	DAP	T-CS/CNI, ABX		OCS	
		57F	None	PDV-PSV	ABX				OCS
O'hagan 1998[58]	5	65F	None	PDV-PSV	OCS	T-CS/CNI + AZA			
Pazheri 2010[59]	5	15F	CD	PSV		T-CS/CNI			
Peuvrel 2008[60]	5	28M	None	PSV			OCS	OCS	
Ruiz-Roca 2005[61]	5	51F	UC	PSV		ABX, T-CS/CNI			
Saghafi 2011[62]	5	30F	None	PSV			OCS		

Shah 2013[63]	5	63M	UC	PSV				DAP	
Soriano 1999[64]	5	49M, White	UC	PDV-PSV		5-ASA, T-CS/CNI	T-CS/CNI + 5-ASA	5-ASA	
Stingeni 2015[65]	5	17M	UC	PSV			OCS	AZA	
Storwick 1994[66]	5	42F	UC	PDV-PSV				OCS	T-CS/CNI, ABX
Thornhill 1992[67]	5	26F, White	UC	PSV			OCS + 5-ASA	DAP	
		51M, White	None	PSV			OCS	ABX + DAP	
		33F, Greek	None	PDV-PSV			OCS	ABX, DAP, AZA	
Tursi 2016[68]	5	42F	UC	PSV	OCS, DAP			BIO, ABX	
Uzuncakmak 2015[69]	5	16M	UC	PDV				OCS, ABX	
Van Hale 1985[70]	5	23F	UC	PDV-PSV	ABX, DAP, MSC	OCS, T-CS/CNI			Colectomy
		24F	UC	PDV-PSV	AZA	T-CS/CNI, IV ALB, MSC	DAP		
Wang 2013[71]	5	42F	UC	PDV-PSV				ALB, OCS	
Werchniak 2005[72]	5	30F	UC	PDV	NYS	T-CS/CNI		5-ASA	
Wolz 2013[73]	5	21M, White	UC	PDV-PSV			T-CS/CNI + DAP	DAP	
		58M, White	CD	PDV-PSV			OCS + DAP	DAP	
Wray 1984[74]	5	58M, White	UC	PSV	5-ASA	OCS			T-CS/CNI
		52M, White	None	PSV					T-CS/CNI + 5-ASA
Yasuda 2008[75]	5	37M	UC	PDV-PSV	T-CS/CNI	Total colectomy		T-CS/CNI	
Index patient	5	51F, Hispanic	UC	PDV-PSV	MTX, T-CS/CNI, ABX, MSC	RET, MM, ABX, T-CS/CNI		DAP, OCS, ABX	

Empty Box: not mentioned or specified in primary paper

Abbreviations: 5-ASA, sulfasalazine/sulphasalazine, aminosalicylates, mesalamine; ABX, antibiotics (piperacillin[4], metronidazole[4,17,37,41], amoxicillin clavulanate[17,18,38,67], dicloxacillin[38], ciprofloxacin[41,42], clarithromycin[42], vancomycin[37], penicillin[44], di-iodohydroxyquinoline[44], streptomycin[44], doxycycline[61], sulfonamides[25,67], and tetracycline[20,21]); ACTH, adrenocorticotropic hormone; ALB, albumin; AZA, azathioprine, mercaptopurine; BIO, biologic (infliximab[3,14,22,31,41], adalimumab[22,48,50], and golimumab[68]); CD, Crohn's disease; CHL, chlorhexidine mouthwash; COL, colchicine; CR-D, complete response-discontinuation; CR-I, complete response—initial; CR-M, complete response—maintenance; DAP, dapsone; F, female; FES, ferrous sulfate; M, male; MM, mycophenolate mofetil; MSC, miscellaneous (intravenous immunoglobulin[7], aurothiomalate[7], acyclovir[12], ketoconazole[3], "antifungals[40]," topical imiquimod, vitamin therapy[70], diphenhydramine elixer[70], and viscous lidocaine[70]); MTX, methotrexate; NYS, nystatin; OCS, systemic corticosteroids; OCNI, oral calcineurin inhibitors; PTR, petrolatum; QoE, quality of evidence; RET, retinoids; T-CS/CNI, topical corticosteroids or topical calcineurin inhibitor; UC, Ulcerative colitis.

"improved but still present," "regressed," or "still mildly active." Cases with complete response required evidence of good control of the disease after initiating or discontinuing the medication. Response of the disease to treatment in these cases was described as: "having marked or significant improvement," "resolution," "relief," or being "well-controlled." Complete response was further subdivided into three categories: resolution while on—initial (CR-I); response while on—maintenance (CR-M); and remission after discontinuation (CR-D). Drugs were split into initial and maintenance categories if one drug resulted in the resolution of lesions (CR-I) then a second drug was added immediately after to maintain remission (CR-M). If a treatment resulted in resolution of PDV-PSV while on the drug, but lesions recurred after discontinuation, then this medication was considered CR-I. A treatment required only intermittently for relapse control resulting in complete control was also considered CR-I. Drugs directed at underlying IBD were generally included in the CR-M category, as patients often remained on these medications indefinitely. Medications that resulted in sustained clearance of PDV-PSV after their discontinuation were considered CR-D. Medications were included in this category if the authors stated that there was "complete remission" after drug discontinuation or sustained clearance was noted after follow-up, with follow-up times ranging from 15 days to 20 years (mean= 26.4 months, median=12 months).

The medications used to treat PDV-PSV were divided as follows: oral corticosteroids (OCS), topical medications (T-CS/CNI), colchicine (COL), azathioprine/6-mercaptopurine (AZA), 5-aminosalicylic-acid (5-ASA) derivatives, oral calcineurin inhibitors (OCNI: tacrolimus and cyclosporine), biologics, oral dapsone (DAP), other antibiotics (ABX), and miscellaneous medications (MSC). Topical corticosteroids and topical tacrolimus were combined into a topical medications category (T-CS/CNI) due to their limited systemic effects. Oral dapsone and other antibiotics were separated because dapsone is most commonly used for its anti-neutrophilic and general anti-inflammatory mechanisms. Other antibiotics used to treat PDV-PSV included: piperacillin[4], metronidazole[4,17,37,41], amoxicillin clavu-lanate[17,18,38,67], dicloxacillin[38], cipro-floxacin[41,42], clarithromycin[42], vancomycin[37], penicillin[44], diiodohydroxyquinoline[44], strep-tomycin[44], doxycycline[61], sulfonamides[25,67], and tetracycline.[20,21] All biologic medications were combined into one category, as they were all TNF alpha blocking agents (infliximab[3,14,22,31,41], adalimumab[22,48,50], and golimumab[68]). Drugs in the miscellaneous category were not included in the statistical analysis because all were used only once. This included intravenous immunoglobulin[7], aurothiomalate[7], acyclovir[12], ketoconazole[3], "antifungals[40]," topical imiquimod, vitamin therapy[70], diphenhydramine elixer[70], and viscous lidocaine.[70]

Statistical Analysis

Each medication was compared across different subgroups to determine if any medications were more successful in patients with certain characteristics. These subgroups included: sex (male versus female), type of inflammatory bowel disease (ulcerative colitis (UC) versus Crohn's disease (CD)), presence of colitis, presence of eosinophilia, presence of elevated inflammatory markers (ESR or CRP), and subtype of PDV-PSV (PDV only versus PDV only versus PDV-PSV). This was done using 2x2 chi square tests to compare the number of times each treatment was successful versus unsuccessful within each subgroup. P-values were adjusted to account for running multiple tests using the Holm method.

RESULTS

In this review, 128 related articles were identified using the search criteria discussed above (Figure 1). After the initial abstract screening 38 articles were excluded. An additional 23 reports were excluded because they did not meet the inclusion criteria for this review. Six additional articles were included from reference lists of PDV-PSV review papers. For the final review, 74 reports were used, which included 72 case reports and 2 case series. This corresponded to 94 unique patients. No prospective or retrospective cohort trials were found for PDV-PSV. With the addition of a patient from the authors' institution, 95 total patients were used in this review an analysis. There was no evidence of duplicate cases.

Demographics of the study population are summarized in Table 2. Seventy-six patients (80%) had concomitant IBD. The median age was 35 (IQR=24) years old and 47 (49%) of the patients were female. The median number of treatments per patient was 2 (IQR=2), with a median follow-up time of up to 12 months (IQR=20).

Several treatments were found to be effective (with greater than 75% of patients having a complete response to the medication), including OCS, AZA, 5-ASA, OCNI, and BIO. T-CS/CNI, Colchicine, oral dapsone, and other antibiotics appeared to have lowest efficacy in treating the disease (Table 3). OCS were the most commonly used treatment, used in 79 of 95 patients (83%). OCS also demonstrated strong efficacy with a complete response achieved in 80% (63/79) patients. OSC was determined to be most successful when used as initial therapy, achieving CR-I in 49% (31/63) of patients achieving complete remission. Topical therapies were used in nearly half of patients (45/95, 47%), but were often unsuccessful, resulting in complete resolution of lesions in only 49% (22/45) of cases. AZA was used by 19 patients (22%) and found to be effective, resulting in CR in 12 (80%) patients. AZA therapy was not found to be more successful in one subgroup of CR over another.

Table 2. Characteristics of the PDV-PSV patients

Characteristics	Values
Total number of patients	95
Female, n (%)	47 (49%)
Median age in years (IQR)	35 (24)
Ethnicity	
White/Caucasian, n (%)	18 (19%)
Other, n (%)	8 (8%)
Unspecified, n (%)	69 (73%)
Associated with IBD/chronic colitis, n (%)	76 (80%)
UC, n (%)	55 (72%)
IBD presented before PDV-PSV, n (%)	56 (74%)
Location of muco-cutaneous lesions	
PSV only, n (%)	46 (48%)
PDV-PSV, n (%)	39 (41%)
PDV only, n (%)	10 (11%)
Peripheral eosinophilia, n (%)	30 (32%)
Elevated inflammatory markers, n (%)	23 (24%)
Median follow up time in months (IQR)	12 (20)
Achieved complete response, n (%)	86 (91%)
Median number of treatments, n (IQR)	2 (2)

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; IQR, interquartile range; PDV, pyodermatitis vegetans; PDV-PSV, pyodermatitis-pyostomatitis vegetans; PSV, pyostomatitis vegetans; UC, ulcerative colitis.

Table 3. Total number of patients per response category by medication class

	Number of within each Response Category (total patients = 95)				Number of Patients within each Complete Response (CR) Subgroup		
Medication	**Total patients (%)**	**No Response (%)**	**Partial Response (%)**	**Complete Response (%)**	**CR-I (% of CR)**	**CR-M (% of CR)**	**CR-D (% of CR)**
OCS	79 (83%)	10 (13%)	6 (9%)	63 (80%)	31 (49%)	23 (23%)	9 (14%)
T-CS/CNI	45 (47%)	10 (22%)	12 (27%)	23 (51%)	6 (26%)	11 (48%)	6 (26%)
DAP	36 (38%)	10 (28%)	5 (14%)	21 (58%)	7 (33%)	13 (62%)	1 (5%)
5-ASA	31 (33%)	5 (16%)	1 (3%)	25 (81%)	3 (12%)	21 (84%)	1 (4%)
ABX	29 (31%)	10 (34%)	4 (14%)	15 (52%)	3 (20%)	7 (47%)	5 (33%)
AZA	19 (20%)	5 (26%)	2 (11%)	12 (63%)	4 (33%)	5 (42%)	3 (25%)
BIO	9 (9%)	2 (22%)	0 (0%)	7 (78%)	1 (14%)	5 (71%)	1 (14%)
COL	6 (6%)	1 (17%)	1 (17%)	4 (67%)	3 (75%)	1 (25%)	0 (0%)
OCNI	4 (4%)	0 (0%)	0 (0%)	4 (100%)	2 (50%)	2 (50%)	0 0%)

Partial response was defined as incomplete resolution of lesions. Complete response required evidence of good control of the disease after initiating or discontinuing the medication. Abbreviations: 5-ASA, sulfasalazine/sulphasalazine, aminosalicylates, mesalamine; ABX, antibiotics; AZA, azathioprine, mercaptopurine; BIO, biologics; COL, colchicine; CR, complete response; CR-D, complete response-discontinuation; CR-I, complete response – initial; CR-M, complete response – maintenance; DAP, dapsone; OCNI, oral calcineurin inhibitors; OCS, systemic corticosteroids; NR, no response; PR, partial response; T-CS/CNI, topical corticosteroids or topical calcineurin inhibitor.

5-ASA was used by 31 (33%) patients and found to be effective, with 25 (81%) patients achieving CR. BIO were used by 9 (9%) patients and also found to effective, resulting in CR in 7 (78%) patients. 5-ASA and BIO were statistically most successful when used as maintenance therapies with 21/25 (84%) and 5/7 (71%) patients achieving a complete response when the therapies were used as maintenance, respectively. OCNI were only used by four (4%) patients, but were still found effective, achieving complete response in 100% of patients. ABX were used in 29 (31%) patients and found to be poorly effective, achieving complete response in only 15 (52%) individuals. DAP was used by 36 (38%) patients and was also found to be ineffective, with 21 (58%) patients achieving any complete response. COL was used by 6 (6%) patients and was found to be ineffective, despite 4/6 (67%) patients achieving complete response.

A comparison of the medications' success within subgroups was analyzed by Chi-squared test. No medications were found to be more successful when treating males versus females, patients with UC versus CD, patients with colitis versus without colitis, patients with versus without eosinophilia prior to initiating therapy, patients with versus without elevated inflammatory markers prior to initiating therapy, and patients with PDV versus PSV versus PDV-PSV.

DISCUSSION

Pyodermatitis-pyostomatitis (PDV-PSV) is a rare mucocutaneous dermatosis characterized by pustular and vegetating lesions of the skin and oral mucosa. In the literature, 80% of cases of PDV-PSV were associated with IBD, though gastrointestinal symptoms may not initially be present. Therefore, the presence of PDV-PSV should trigger further investigation for underlying IBD.[16,35] The proposed mechanism and disease process of PDV-PSV remains unknown. While the name "pyoderma" suggests skin infection, no consistent pathogenic bacteria, fungi, or viruses have

been discovered.[48] Thus, PDV-PSV is thought to result from an abnormal inflammatory response to unknown factors. Due to the high proportion of PDV-PSV cases associated with IBD, these factors are hypothesized to be antigens shared by bacteria in both the gut and the skin.

Multiple treatment options exist for PDV-PSV, primarily targeting underlying IBD and the pathologic cutaneous inflammatory response. Unfortunately, due to the rarity of PDV-PSV, no controlled trials exist comparing different treatment modalities. Healey et al published an initial treatment algorithm for only PSV in 1994.[29] Consequently, drugs like biologics and calcineurin inhibitors, more commonly used now than 26 years ago, were not represented.

The present review of treatment data from 95 cases provides updated evidence regarding the most effective therapies. Multiple therapies are often required with widely varying levels of success. In the present review, many patients had success with oral corticosteroids when used initially, either followed by steroid-sparing maintenance therapy or when used intermittently for relapse control. Improvement in skin and oral lesions generally correlated with treatment of underlying IBD, likely because of shared pathogenesis involving overactive inflammatory response.[1,5,11,15,16,29,61,65,66]

The results suggest that a patient, with or without IBD, may see benefit with a course of OCS as the initial intervention. In patients with active IBD, 5-ASA may be helpful in managing both the IBD and mucocutaneous symptoms. 5-ASA can also be attempted if OCS fail to result in remission for patients without associated IBD, as the data does not suggest an increased efficacy in IBD associated PDV-PSV versus skin only disease. Maintenance therapy can also be initiated if a patient is requiring frequent courses of OCS due to relapse of the disease. While topical steroids are currently considered first line treatment based on Healey's treatment algorithm, the data clearly demonstrates PDV-PSV responds poorly to topical medications. Oral dapsone and colchicine are also commonly used but demonstrate poor efficacy for the treatment of PDV-PSV. Antibiotics were found to be ineffective medications for the treatment of PDV-PSV but should be considered if there is concern for superinfection.

If the above medications fail, are poorly tolerated, or the provider or patient prefers, azathioprine or 6-mercaptopurine or an oral calcineurin inhibitor may be attempted for patients with or without associated IBD. In refractory cases, a TNF-alpha blocking biologic can be used. Given their safety and significant effectiveness as maintenance therapies, biologics can also be considered earlier in the treatment course. However, data is limited by small sample size.

This review has several limitations. First, there are no prospective studies regarding the treatment of PDV-PSV due to the rarity of the disease, so this analysis is limited to case reports and case series. This lends to both publication and reporting bias. Reports were likely not written and/or published if medications used to treat PDV-PSV were ineffective, leading to a lack of negative data. Additionally, studies may have selectively reported only positive outcomes, and there was no standardized way of reporting these outcomes. Due to this lack of standardization of the magnitudes of the responses to the medications, response categories were created based on the specific phrases used in the primary literature. This made the vocabulary used in each article extremely important, as specific wording was

categorized as different levels of response. This use of categorization based on semantics is inherent in retrospective papers, as well as review papers. Prospective data and controlled studies would be necessary to fully compare different regimens.

Furthermore, the reviewers grouped medications (such as topical medications and biologics) into classes for statistical analysis due to small sample sizes. This could mask the effects of individual agents. Finally, follow-up time varied greatly (mean=28.3 months, range=1-252 months), thus making it difficult to determine long-term effects. Some patients had no follow up or were seen as early as one-week post discontinuation of their medication(s). Some papers did not record follow up results at all. Because of this variation in follow-up reported, the maintenance of remission following discontinuation of a medication could not always be determined.

CONCLUSION

When a patient is diagnosed with PDV-PSV, it is important to evaluate for underlying IBD due to the high number of associated cases. No treatments proved to be more or less effective for IBD associated PDV-PSV versus skin-only disease, but PDV-PSV improvement tended to correlate with management of associated IBD if present. Oral corticosteroids were the most commonly used and most effective medication at obtaining resolution of the mucocutaneous lesions of pyodermatitis-pyostomatitis vegetans. Based on the literature review conducted, other effective treatments include azathioprine and 6-mercaptopurine, 5-aminiosalicylic acid derivatives, oral calcineurin inhibitors, and TNF-alpha blocking biologics. It will be important to improve the evidence for the efficacy of these medications through rigorous prospective studies.

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References:

1. Hegarty AM, Barrett AW, Scully C. Pyostomatitis vegetans. Clin Exp Dermatol. 2004 Jan;29(1):1–7.
2. Mccarthy P, Shklar G. A SYNDROME OF PYOSTOMATITIS VEGETANS AND ULCERATIVE COLITIS. Arch Dermatol. 1963 Dec;88:913–9.
3. Clark LG, Tolkachjov SN, Bridges AG, Camilleri MJ. Pyostomatitis vegetans (PSV)-pyodermatitis vegetans (PDV): A clinicopathologic study of 7 cases at a tertiary referral center. J Am Acad Dermatol. 2016 Sep;75(3):578–84.
4. Bianchi L, Carrozzo AM, Orlandi A, Campione E, Hagman JH, Chimenti S. Pyoderma vegetans and ulcerative colitis. Br J Dermatol. 2001 Jun;144(6):1224–7.
5. Mehravaran M, Kemény L, Husz S, Korom I, Kiss M, Dobozy A. Pyodermatitis-pyostomatitis vegetans. Br J Dermatol. 1997 Aug;137(2):266–9.
6. Brunsting LA, Underwood LJ. Pyoderma vegetans in association with chronic ulcerative colitis. Arch Dermatol Syphilol. 1949 Aug;60(2):161–72.
7. Abellaneda C, Mascaró JM, Vázquez MG, Pablo IM-D, Iranzo P. All that glitters is not pemphigus: Pyodermatitis-pyostomatitis vegetans misdiagnosed as IgA pemphigus for 8 years. Am J Dermatopathol. 2011 Feb;33(1):e1-6.
8. Ahn BK, Kim S-C. Pyodermatitis-pyostomatitis vegetans with circulating autoantibodies to

bullous pemphigoid antigen 230. J Am Acad Dermatol. 2004 May;50(5):785–8.
9. Al-Rimawi HS, Hammad MM, Raweily EA, Hammad HM. Pyostomatitis vegetans in childhood. Eur J Pediatr. 1998 May;157(5):402–5.
10. Atarbashi-Moghadam S, Lotfi A, Atarbashi-Moghadam F. Pyostomatitis Vegetans: A Clue for Diagnosis of Silent Crohn's Disease. J Clin Diagn Res JCDR. 2016 Dec;10(12):ZD12–3.
11. Ayangco L, Rogers RS, Sheridan PJ. Pyostomatitis vegetans as an early sign of reactivation of Crohn's disease: a case report. J Periodontol. 2002 Dec;73(12):1512–6.
12. Ballo FS, Camisa C, Allen CM. Pyostomatitis vegetans. Report of a case and review of the literature. J Am Acad Dermatol. 1989 Aug;21(2 Pt 2):381–7.
13. Bens G, Laharie D, Beylot-Barry M, Vergier B, Noblesse I, Beylot C, et al. Successful treatment with infliximab and methotrexate of pyostomatitis vegetans associated with Crohn's disease. Br J Dermatol. 2003 Jul;149(1):181–4.
14. Bertlich I, Gauss A, Schäkel K, Enk A, Hoffmann JHO. Pyodermatitis-pyostomatitis vegetans with histological and immunohistological aspects of autoimmune blistering disease treated with infliximab. J Dtsch Dermatol Ges J Ger Soc Dermatol JDDG. 2019;17(5):540–2.
15. Brinkmeier T, Frosch PJ. Pyodermatitis-pyostomatitis vegetans: a clinical course of two decades with response to cyclosporine and low-dose prednisolone. Acta Derm Venereol. 2001 May;81(2):134–6.
16. Calobrisi SD, Mutasim DF, McDonald JS. Pyostomatitis vegetans associated with ulcerative colitis. Temporary clearance with fluocinonide gel and complete remission after colectomy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1995 Apr;79(4):452–4.
17. Canpolat F, Cemil BÇ, Yılmazer D, Yeşilli O, Eskioğlu F. Pyoderma vegetans associated with ulcerative colitis: a case with good response to steroids. Case Rep Dermatol. 2011 Mar 26;3(1):80–4.
18. Carvalho S, Sanches M, Alves R, Selores M. Pyodermatitis vegetans of the vulva. Dermatol Online J. 2016 Jun 16;22(6).
19. Cataldo E, Covino MC, Tesone PE. Pyostomatitis vegetans. Oral Surg Oral Med Oral Pathol. 1981 Aug;52(2):172–7.
20. Chan SW, Scully C, Prime SS, Eveson J. Pyostomatitis vegetans: oral manifestation of ulcerative colitis. Oral Surg Oral Med Oral Pathol. 1991 Dec;72(6):689–92.
21. Chaudhry SI, Philpot NS, Odell EW, Challacombe SJ, Shirlaw PJ. Pyostomatitis vegetans associated with asymptomatic ulcerative colitis: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999 Mar;87(3):327–30.
22. Dodd EM, Howard JR, Dulaney ED, Rosenthal SI, Wanna MR, Farah RS. Pyodermatitis-pyostomatitis vegetans associated with asymptomatic inflammatory bowel disease. Int J Dermatol. 2017;56(12):1457–9.
23. Dupuis EC, Haber RM, Robertson LH. Pyoblepharitis Vegetans in Association With Pyodermatitis-Pyostomatitis Vegetans: Expanding the Spectrum of a Rare, Multisystem Disorder. J Cutan Med Surg. 2016 Apr;20(2):163–5.
24. Ficarra G, Cicchi P, Amorosi A, Piluso S. Oral Crohn's disease and pyostomatitis vegetans. An unusual association. Oral Surg Oral Med Oral Pathol. 1993 Feb;75(2):220–4.
25. Forman L. TWO CASES OF PYODERMITE VEGETANTE (HALLOPEAU): AN EOSINOPHILIC PUSTULAR AND VEGETATING DERMATITIS WITH CONJUNCTIVAL, ORAL AND COLONIC INVOLVEMENT. Proc R Soc Med. 1965 Apr;58:244–9.
26. Gonzalez-Moles MA, Gil-Montoya JA, Ruiz-Avila I, Esteban F, Bascones-Martinez A. Pyostomatitis vegetans: dramatic clinical response to clobetasol propionate treatment in aqueous solution. J Eur Acad Dermatol Venereol JEADV. 2008 Feb;22(2):252–3.
27. Hansen LS, Silverman S, Daniels TE. The differential diagnosis of pyostomatitis vegetans and its relation to bowel disease. Oral Surg Oral Med Oral Pathol. 1983 Apr;55(4):363–73.
28. Harish K, Varghese T, Najeeba R, Harikumar R. Pyoderma vegetans and ulcerative colitis. J Postgrad Med. 2006 Dec;52(4):302–3.
29. Healy CM, Farthing PM, Williams DM, Thornhill MH. Pyostomatitis vegetans and associated systemic disease. A review and two case reports. Oral Surg Oral Med Oral Pathol. 1994 Sep;78(3):323–8.
30. Kajihara I, Ichihara A, Higo J, Kidou M, Ihn H. Pyodermatitis vegetans associated with multiple myeloma. J Dermatol. 2013 Mar;40(3):222–3.
31. Kalman RS, Gjede JM, Farraye FA. Pyostomatitis vegetans in a patient with fistulizing Crohn's disease. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2013 Dec;11(12):A24.
32. Khader A, Ambooken B, Muhammed K, Binitha MP, Sureshan DN, Manakkad SP. Pyodermatitis-pyostomatitis Vegetans with Penile Ulceration

Complicated by Acute Glomerulonephritis. Indian J Dermatol. 2016 Apr;61(2):239.
33. Kim TH, Kim S-C. Pyodermatitis-Pyostomatitis Vegetans Associated with Crohn's Disease. Ann Dermatol. 2015 Oct;27(5):624–5.
34. Kitayama A, Misago N, Okawa T, Iwakiri R, Narisawa Y. Pyodermatitis-pyostomatitis vegetans after subtotal colectomy for ulcerative colitis: Pyodermatitis-pyostomatitis vegetans. J Dermatol. 2010 Jul 22;37(8):714–7.
35. Knapp N, Khan Z, Albuquerque R, Richards A, Brown RM. Pyostomatitis Vegetans in Ulcerative Colitis; Management with Topical Tacrolimus and Systemic Azathioprine in a 10-year-old Boy (Case Report and Review of the Literature). J Int Oral Health. 2015 Aug 15;8(1):132–6.
36. Ko H-C, Jung D-S, Jwa S-W, Cho H-H, Kim B-S, Kwon K-S, et al. Two cases of pyodermatitis-pyostomatitis vegetans. J Dermatol. 2009 May;36(5):293–7.
37. Konstantopoulou M, O'Dwyer EM, Steele JC, Field EA, Lewis M a. O, Macfarlane AW. Pyodermatitis–pyostomatitis vegetans complicated by methicillin-resistant Staphylococcus aureus infection. Clin Exp Dermatol. 2005;30(6):666–8.
38. Leibovitch I, Ooi C, Huilgol SC, Reid C, James CL, Selva D. Pyodermatitis-pyostomatitis vegetans of the eyelids case report and review of the literature. Ophthalmology. 2005 Oct;112(10):1809–13.
39. Li S, Li Z, Feng S. Low-dose sulfasalazine in a case of Pyodermatitis-pyostomatitis Vegetans. J Am Acad Dermatol. 2018 Oct 20;
40. Lopez-Jornet P, Gomez-Garcia F, Camacho-Alonso F. Pyostomatitis vegetans. Clinical marker of ulcerative colitis. N Y State Dent J. 2012 Mar;78(2):36–7.
41. Lourenço SV, Hussein TP, Bologna SB, Sipahi AM, Nico MMS. Oral manifestations of inflammatory bowel disease: a review based on the observation of six cases. J Eur Acad Dermatol Venereol JEADV. 2010 Feb;24(2):204–7.
42. Maseda R, Rodriquez AI, Feito M, De Lucas R. A case of pyoderma vegetans associated with Crohn's disease under adalimumab. J Am Acad Dermatol. 2017 Jun;76(6):AB8.
43. Markiewicz M, Suresh L, Margarone J, Aguirre A, Brass C. Pyostomatitis Vegetans: A Clinical Marker of Silent Ulcerative Colitis. J Oral Maxillofac Surg. 2007 Feb;65(2):346–8.
44. Gold S. Ulcerative colitis with pyodermite vegetante. Proc R Soc Med. 1962 Dec;55:1072–3.
45. Matias F de AT, Rosa DJ de F, Carvalho MTF de, Castañon MCMN. Pyodermatitis-pyostomatitis vegetans: case report and review of medical literature. An Bras Dermatol. 2011 Aug;86(4 Suppl 1):S137-140.
46. Merkourea SS, Tosios KI, Merkoureas S, Sklavounou-Andrikopoulou A. Pyostomatitis vegetans leading to Crohn's disease diagnosis. Ann Gastroenterol. 2013;26(2):187.
47. Mesquita K de C, Costa IMC. Case for diagnosis. An Bras Dermatol. 2012 Dec;87(6):929–31.
48. Mijandrusić-Sincić B, Licul V, Gorup L, Brncić N, Glazar I, Lucin K. Pyostomatitis vegetans associated with inflammatory bowel disease--report of two cases. Coll Antropol. 2010 Apr;34 Suppl 2:279–82.
49. Mizukami Y, Imanishi H, Tateishi C, Kaneshiro S, Sowa-Osako J, Ohsawa M, et al. Successful treatment of pyostomatitis vegetans with ulcerative colitis using dapsone without systemic steroids. J Dermatol. 2019;46(9):e316–7.
50. Molnár T, Farkas K, Nagy F, Vass N, Szepes Z, Tiszlavicz L, et al. Third case: Another pediatric patient with pyostomatitis vegetans and oral granuloma as one of the initial symptoms of Crohn's disease: Inflamm Bowel Dis. 2011 Sep;17(9):E122–3.
51. Moloney G, Dolman PJ. Eyelid deformities from pyodermatitis pyostomatitis vegetans: Letter to the Editor. Clin Experiment Ophthalmol. 2011 Dec;39(9):910–1.
52. Naish JM, Batchvarov BD, Lawoyin VL. A case of ulcerative colitis and pyostomatitis vegetans in an African. Gut. 1970 Jan;11(1):38–40.
53. Nayak S, Patro S. Pyodermatitis-pyostomatitis vegetans. Indian J Dermatol. 2017;62(4):434.
54. Neville BW, Smith SE, Maize JC, Laden SA, Denton WT. Pyostomatitis vegetans. Am J Dermatopathol. 1985 Feb;7(1):69–77.
55. Nico MMS, Hussein TP, Aoki V, Lourenço SV. Pyostomatitis vegetans and its relation to inflammatory bowel disease, pyoderma gangrenosum, pyodermatitis vegetans, and pemphigus. J Oral Pathol Med Off Publ Int Assoc Oral Pathol Am Acad Oral Pathol. 2012 Sep;41(8):584–8.
56. Niezgoda A, Białecka A, Marek-Józefowicz L, Skrzeczko-Kwela E, Czajkowski R. Pyoderma gangrenosum with its subtype affecting oral mucosa pyostomatitis vegetans following skin melanoma surgical excision in a patient with ulcerative colitis: a case report. Postepy Dermatol Alergol. 2018 Apr;35(2):212–6.
57. Nigen S, Poulin Y, Rochette L, Lévesque M-H, Gagné E. Pyodermatitis-pyostomatitis vegetans:

two cases and a review of the literature. J Cutan Med Surg. 2003 Jun;7(3):250–5.
58. O'Hagan AH, Irvine AD, Allen GE, Walsh M. Pyodermatitis-pyostomatitis vegetans: evidence for an entirely mucocutaneous variant. Br J Dermatol. 1998 Sep;139(3):552–3.
59. Pazheri F, Alkhouri N, Radhakrishnan K. Pyostomatitis vegetans as an oral manifestation of Crohn's disease in a pediatric patient. Inflamm Bowel Dis. 2010 Dec;16(12):2007.
60. Peuvrel L, Barbarot S, Gagey-Caron V, Tessier M-H, Cassagnau E, Stalder J-F. [Pyodermatitis-pyostomatitis vegetans with nasal involvement]. Ann Dermatol Venereol. 2008 Nov;135(11):753–6.
61. Ruiz-Roca JA, Berini-Aytés L, Gay-Escoda C. Pyostomatitis vegetans. Report of two cases and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005 Apr;99(4):447–54.
62. Saghafi S, Falaki F, Bashardoost N. Pyostomatitis vegetans: report of a rare case. Pol J Pathol Off J Pol Soc Pathol. 2011;62(2):125–8.
63. Shah S, Cotliar J. Pyostomatitis Vegetans. N Engl J Med. 2013 May 16;368(20):1918–1918.
64. Soriano ML, Martínez N, Grilli R, Fariña MC, Martín L, Requena L. Pyodermatitis-pyostomatitis vegetans: report of a case and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999 Mar;87(3):322–6.
65. Stingeni L, Tramontana M, Bassotti G, Bianchi L, Lisi P. Pyodermatitis-pyostomatitis vegetans and antibullous pemphigoid antigen 180 autoantibodies: a casual association? Br J Dermatol. 2015 Mar;172(3):811–3.
66. Storwick GS, Prihoda MB, Fulton RJ, Wood WS. Pyodermatitis-pyostomatitis vegetans: A specific marker for inflammatory bowel disease. J Am Acad Dermatol. 1994 Aug;31(2):336–41.
67. Thornhill MH, Zakrzewska JM, Gilkes JJH. Pyostomatitis vegetans: report of three cases and review of the literature. J Oral Pathol Med. 1992 Mar;21(3):128–33.
68. Tursi A. Concomitant hidradenitis suppurativa and pyostomatitis vegetans in silent ulcerative colitis successfully treated with golimumab. Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver. 2016 Dec;48(12):1511–2.
69. Uzunçakmak T, Akdeniz N, Karadağ A, Çobanoğlu B. Pyodermatitis vegetans after total colectomy. Indian Dermatol Online J. 2015;6(7):9.
70. VanHale HM, Rogers RS, Zone JJ, Greipp PR. Pyostomatitis vegetans. A reactive mucosal marker for inflammatory disease of the gut. Arch Dermatol. 1985 Jan;121(1):94–8.
71. Wang H, Qiao S, Zhang X, Liu C. A case of pyodermatitis-pyostomatitis vegetans. Am J Med Sci. 2013 Feb;345(2):168–71.
72. Werchniak AE, Storm CA, Plunkett RW, Beutner EH, Dinulos JGH. Treatment of pyostomatitis vegetans with topical tacrolimus. J Am Acad Dermatol. 2005 Apr;52(4):722–3.
73. Wolz MM, Camilleri MJ, McEvoy MT, Bruce AJ. Pemphigus vegetans variant of IgA pemphigus, a variant of IgA pemphigus and other autoimmune blistering disorders. Am J Dermatopathol. 2013 May;35(3):e53-56.
74. Wray D. Pyostomatitis vegetans. Br Dent J. 1984 Nov 10;157(9):316–8.
75. Yasuda M, Amano H, Nagai Y, Tamura A, Ishikawa O, Yamaguchi S. Pyodermatitis-Pyostomatitis Vegetans Associated with Ulcerative Colitis: Successful Treatment with Total Colectomy and Topical Tacrolimus. Dermatology. 2008;217(2):146–8