Epidemiology of Pemphigus

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Pemphigus is an epidemiologically heterogeneous group of autoimmune bullous diseases comprising pemphigus vulgaris (PV), pemphigus foliaceus, paraneoplastic pemphigus, IgA pemphigus, and pemphigus herpetiformis. Recently, our knowledge about the frequency of pemphigus, which is highly variable between different populations, has considerably expanded, and the first non-HLA genes associated with PV have been identified. In addition, a variety of comorbidities, including other autoimmune diseases, hematological malignancies, and psoriasis, have been described in this variant. Here, initial data about the impact of COVID-19 on this fragile patient population are discussed and perspectives for future epidemiological studies are outlined.

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Introduction

Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are the two major types of pemphigus. PV is immunologically characterized by autoimmunity against desmoglein (DSG) 3, a structural protein of the epidermal and epithelial desmosome, and clinically presents with erosions on mucosal surfaces (Schmidt et al., 2019). In about half of patients with PV, additional autoantibodies against DSG1 are observed, and mucosal lesions are accompanied by flaccid blisters and erosions on the skin. In contrast, patients with PF only generate autoantibodies against DSG1, and lesions are limited to the skin (Kasperkiewicz et al., 2017; Schmidt et al., 2019). The therapeutic mainstay is systemic corticosteroids that are usually combined with potentially corticosteroid-sparing agents, such as azathioprine and mycophenoles. Following the licensing of the anti-CD20 antibody rituximab by the European Medicines Agency (EMA) and the United States Food and Drug Administration for moderate and severe PV, the use of rituximab as first line treatment for moderate-to-severe PV and PF is recommended (Joly et al., 2020; Murrell et al., 2020).

The relative distribution of PV and PF varies in different countries. Out of all patients with pemphigus, the frequency of PV ranges between 13% (in Mali) and 95% (in Saudi Arabia) (Mahé et al., 1996; Tallab et al., 2001). In Europe and Northern America, 65–90% of pemphigus cases are PV, which was reviewed in Kridin (2018). The much higher incidence of PF than of PV in well-defined regions in South America and North Africa has inspired the term endemic PF.

The epidemiology of paraneoplastic pemphigus (PNP), a rare pemphigus variant accounting for about 5% of pemphigus cases (Jelti et al., 2019), is summarized later. IgA pemphigus, which was reviewed in Hashimoto et al. (2017), and pemphigus herpetiformis, which was reviewed in Kasperkiewicz et al. (2014), are even considerably less frequent, with few epidemiological data available. In about a quarter of patients with the subcorneal pustular dermatosis type of IgA pemphigus, a monoclonal IgA gammopathy can be detected (Kridin et al., 2020b; Tsuruta et al., 2011).

Age and gender

Pemphigus can arise in any age group with most patients aged between 45 and 65 years at the time of diagnosis (Table 1). Outside the endemic areas, where up to 30% of patients have been reported to be younger than 20 years (Aoki et al., 2015; Diaz et al., 1989), pemphigus is rare aged below 18 years (Hübner et al., 2020; Mintz and Morel, 2011). In a recent study from Germany, only 0.6% of patients with PV were minors (Hübner et al., 2020, 2016). The mean age of presentation in PV ranges between 36.5 years in Kuwait (Nanda et al., 2004) and 72.4 years in Bulgaria (Tsankov et al., 2000).

Apart from two studies originating from Kuwait (Nanda et al., 2004) and Saudi Arabia (Tallab et al., 2001), a female preponderance was reported in all the remaining study cohorts of nonendemic pemphigus, with the female-to-male ratio mainly ranging between 1 and 2, with 5.0 in the United States (Simon et al., 1980) (Table 1). It is noteworthy that women aged between 25 and 34 years are predominantly affected in endemic PF in Tunisia (Morini et al., 1993).

Incidence

Multiple lines of evidence suggest that PV displays a heterogeneous geographic and ethnic distribution. The annual incidence rates of PV range between 0.76 cases per million in Finland (Hietanen and Salo, 1982) and 32.0 cases per million among Jewish individuals in the United States (Simon et al., 1980) (Table 1). A prominent predisposition to PV was observed in certain ethnic groups, namely in individuals of Ashkenazi Jewish and Mediterranean ancestries. Correspondingly, the three highest annual incidence rates of PV

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Abbreviations: ACE, angiotensin-converting enzyme; AIBD, autoimmune bullous disease; CAAR, chimeric autoantibody receptor; CI, confidence interval; DSG, desmoglein; EADV, European Academy of Dermatology and Venereology; EC, extracellular; EMA, European Medicines Agency; FS, fogo selvage; HR, hazard ratio; ICD, International Classification of Diseases; PF, pemphigus foliaceus; PNP, paraneoplastic pemphigus; PV, pemphigus vulgaris; SMR, standardized mortality ratio

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Table 1. Demographic Features and Incidence Rates of Pemphigus in Different Countries across the World

Country	Region	Time Period (y)	Number of Patients	F-to-M Ratio	Mean Age, y	Annual Incidence Rate (/Million)
Botswana (Madu et al., 2019)	Gaborone, Kanye, Mochudi, Lobatse, Mahalapye	2008–2015	15	ND	ND	1.7 (0.9 [PF]; 0.8 [PV[1]])
Bulgaria (Tsankov et al., 2000)	Sofia	1980–1995	74	1.2	72.4	4.7
Croatia (Marinovic et al., 2011)	Zagreb	2005–2010	41	1.9	ND	3.7
Finland (Hietanen and Salo, 1982)	Nationwide	1969–1978	44	1.1	57.5	0.8
France (Bastuji-Garin et al., 1995)	Ile-de-France administrative area	1985–1990	87	1.2	52	1.7
France (Thomas et al., 2010)	Midi-Pyrénées region	2002–2006	37	1.2	62	2.7
France (Jelti et al., 2019)	13 regions in France	2004–2013	249	1.07	59	1.5
Germany (Hahn-Ristic et al., 2002)	Würzburg and Mannheim	1989–1997	14	1.3	ND	0.8 (PV in native Germans); 6.8 (PV in foreigners)
Germany (Bertram et al., 2009)	lower Franconia	2001–2002	1	ND	62	0.5 (PV)
Greece (Michailidou et al., 2007)	Thessaloniki	1985–2004	129	2.3	59.6	8.0 (PV)
India (Kumar, 2008)	Thrissur District	2001	13	2.3	37 (F), 58 (M)	4.4
Israel (Pisanti et al., 1974)	Jerusalem	1952–1972	76	1.6	ND	16.1 (PV)
Israel (Kridin et al., 2016)	Haifa	2000–2015	180	1.7	54.7	7.2
Iran (Chams-Davatchi et al., 2005)	Tehran	1984–2003	1,209	1.5	42	16.0 (Tehran District), 10.0 (Iran)
Iran (Salmanpour et al., 2006)	Shiraz	1991–2000	221	1.3	38	6.7
Italy (Micali et al., 1998a)	Sicily	1982–1996	84	1.6	56	6.0
Kuwait (Nanda et al., 2004)	Kuwait city (covering 50% of the population of Kuwait)	1991–2002	60	0.9	36.5	4.6
Macedonia (V'lckova-Laskoska et al., 2007)	Skopje (covering all the population)	1990–2004	133	1.3	52	4.4
Malaysia (Adam, 1992)	Kuala Lutnpur	ND	84	1	ND	2.0
Mali (Mahé et al., 1996)	Bamako	ND	30	4	46.7	2.9
Poland (Serwin et al., 2018)	Podlaskie Province	2001–2015	66	2.9	55	3.7
Romania (Baican et al., 2010)	Northwestern Romania	2001–2007	68	1.8	53	4.0
Saudi Arabia (Tallab et al., 2001)	Southern region	1990–1999	19	0.5	43.1	1.6
Serbia (Golušin et al., 2005)	Vojvodina	1990–2002	51	1.55	55.6	6.6
Serbia (Milinković et al., 2016)	Central Serbia	1991–2010	478	1.4	ND	4.0[2]
South Korea (Lee et al., 2018)	Nationwide	2006–2015	1,604	1.2 (PV); 0.9 (PF)	ND	2.1 (PV); 1.1 (PF)
Spain (Grau-Pérez et al., 2019)	Canary Islands	2004–2017	9 (PV); 15 (PF)	2.0 (PV); 0.5 (PF)	51.1 (PV); 51.3 (PF)	5.9
Switzerland (Marazza et al., 2009)	Nationwide	2001–2002	7	2.5	62.3	0.6
Taiwan (Huang et al., 2012)	Nationwide	2002–2009	853	1.3	52.5	4.7
Taiwan (Chiu et al., 2020)	Nationwide	2010–2015	1,207	1.2	53.0	4.0
Tunisia (Morini et al., 1993)	Sousse area	1985–1987	20	F only	28.0 (PF)	4.0 (PF)
Tunisia (Bastuji-Garin et al., 1995)	Nationwide	1986–1991	198	4	36.7	6.7
Tunisia (Zaraa et al., 2011)	Northern Tunisia	1997–2007	92	2	50	8.6
Turkey (Uzun et al., 2006)	Adana and Antalya	1998–2004	148	1.5	43	2.4
Turkey (Bozdag and Bilgin, 2012)	Aydn	1998–2009	87	1.6	48	1.8
Turkey (Yayli et al., 2017)	All regions of the country	2013–2014	220	1.4	49	4.7
United Kingdom (Langan et al., 2008)	Nationwide	1996–2006	138	1.9		6.8 (PV)
United States (Simon et al., 1980)	Connecticut	1972–1977	12	5	63.6	4.2 (general population), 32 (among Jews)

Abbreviations: F, female; M, male; ND, nondetermined; PF, pemphigus foliaceus.; PV, pemphigus vulgaris.

Annual incidence rates were estimated as ratios of the number of newly diagnosed cases of pemphigus in the catchment area of the study over the mean population size in the middle year of each study (population sizes were obtained from the national censuses). Unadjusted incidence rates were adopted because only a minority of studies reported adjusted incidence rates, and the latter used various standardized populations as a reference.

[1]Including pemphigus vegetans.

[2]Age-adjusted incidence rate.

worldwide were registered in Tehran District, Iran (16.0 per million) (Chams-Davatchi et al., 2005) and among the Jewish population in Jerusalem, Israel (16.1 per million) (Pisanti et al., 1974) and Connecticut (32.0 per million) (Simon et al., 1980). In a recent population-based study, the risk of PV was increased 3.6-fold among Jews relative to Arabs in Northern Israel (Kridin et al., 2017a). Simon et al. (1980) reported more than a seven-fold elevated incidence of PV in people of Jewish descent relative to their non-Jewish counterparts.

Sporadic PF is an infrequent disease, corresponding to the minority of pemphigus cases in most study populations (Kridin, 2018). Its annual incidence in the Western world is estimated at <1 case per million (Schmidt et al., 2016). The annual incidence rate of PF in South Korea was 1.1 per million (Lee et al., 2018) and in Northern Israel was 0.8 per million, with no evident ethnic predilection (Kridin et al., 2017a). An association with HLA-DRB1*0101 was observed among Mexican patients with sporadic PF (del Mar Sáez-de-Ocariz et al., 2005).

Prevalence

Data about prevalence in pemphigus are scarce. In the Danish National Patient Registry, the prevalence of pemphigus was calculated to be 60 per million in 2006. Based on data from the largest German health insurance, the prevalence of pemphigus was estimated to be 148 per million individuals in 2014 and 53 per million children and/or adolescents in 2015 (Hübner et al., 2020, 2016). For PV and PF, prevalence rates of 95 per million and 10 per million were reported in the latter study (Hübner et al., 2016).

Endemic PF

In some rural areas in South America (Brazil, Northern Colombia, and Peru) and Northern Africa, PF is not only the predominant pemphigus variant but also occurs more frequently in the population. In southern parts of Tunisia the annual incidence of PF was estimated at 4.0 per million (Bastuji-Garin et al., 1995). In well-studied areas of southeastern Brazil, where it is called fogo selvagem meaning burning fire, the prevalence of PF reached 3% of the population in the 1980s and 1990s but has considerably declined since then (Aoki et al., 2015; Diaz et al., 1989; Warren et al., 2000). There is no sex or racial predisposition. Most patients live in poor hygiene and housing conditions. The decreased prevalence of endemic PF in the states of Sao Paulo, Mato Grosso do Sul, and Parana was linked to improved living conditions (Diaz et al., 1989; Empinotti et al., 2006). Similar to the Braziliensis type, most patients with Columbian endemic PF are illiterate and poor and perform outdoor activities. The prevalence of the disease among the rural population was 2.3% between 1992 and 2001 (Abrèu-Velez et al., 2003). Of note, 95% of the patients were men, and the remaining 5% were postmenopausal women (Abrèu-Velez et al., 2003).

Mortality

The advent of corticosteroids in the early 1950s revolutionized the prognosis of pemphigus and led to a drastic decline in the mortality of patients, particularly those with PV, from 75% to 30% (Bystryn and Steinman, 1996). The increasing utilization of adjuvant corticosteroid-sparing immunosuppressants since the 1980s, which enabled a quicker tapering of systemic corticosteroids, bore an additional decline in mortality to below 5% (Bystryn and Steinman, 1996; Risser et al., 2009; Uzun et al., 2006). In a recent registry-based study, patients with a secondary diagnosis of pemphigus had significantly higher inpatient mortality (3.2%) than those with a primary (1.6%) or no (1.8%) diagnosis of pemphigus (Hsu et al., 2016b). Congruently, in a retrospective Israeli study encompassing 245 patients with pemphigus, the 1-, 5-, 10-, 15-, and 20-year overall survival rates were 95.8%, 93.4%, 89.7%, 79.2%, and 66.3%, respectively (Kridin et al., 2017b). In a French multicenter study including 249 patients with pemphigus, the 1-, 2-, and 5-year overall survival rates were 92%, 88%, and 77%, respectively (Jelti et al., 2019). These three studies signify that pemphigus-associated mortality stems chiefly from late and long-term complications rather than from direct and early activity of the disease.

Despite the aforementioned decline throughout the years, the mortality of patients with pemphigus nowadays remains excessive as compared with the general population. In a British population-based study using a computerized dataset, mortality among patients with PV was 3.3 times higher than among age- and sex-matched control subjects (Langan et al., 2008). The standardized mortality ratios (SMRs) of patients with pemphigus were calculated at 1.7 (Jelti et al., 2019), 2.4 (Huang et al., 2012; Kridin et al., 2017b), and 3.6 (Chiu et al., 2020) in population-based studies originating from France, Israel, and Taiwan, respectively. The latter findings denote that patients with pemphigus were 1.7−3.6 times as likely to die as their age- and sex-matched local counterparts.

PF usually follows a more favorable prognosis than PV. In contrast to the potentially devastating nature of PV, PF is typified by a more benign and chronic course that tends to persist for months to years (Ahmed and Moy, 1982). In a recent population-based study originating from Israel, the mortality among patients with PF was not significantly increased as compared with the age- and sex-matched general population (SMR = 1.4; 95% confidence interval [CI] = 0.6−2.9) (Kridin et al., 2017a). In the same study, the overall survival rates at 1, 5, 10, 15, and 20 years were estimated to be 100%, 96.7%, 92.5%, 81.2%, and 81.2%, respectively (Kridin et al., 2017a). Nonetheless, a recent Korean study revealed a significantly increased SMR among patients with PF (4.8) (Lee et al., 2018).

Infections, mainly pneumonia and septicemia, were the leading causes of death in different study populations (Ahmed and Moy, 1982; Chams-Davatchi et al., 2005; Huang et al., 2012; Kridin et al., 2017a). Only two epidemiological studies, however, estimated the relative risk of mortality owing to different causes (Huang et al., 2012; Kridin et al., 2017b). These Israeli and Taiwanese studies evaluated the cause-specific SMRs in pemphigus and thus enabled investigating the risk of death owing to different causes relative to the general population. In Israel, the risk of infection-associated mortality was 22.6-fold higher than in the matched general population (Kridin et al., 2017b). Compared with the general population, patients with pemphigus displayed an elevated mortality risk because of pneumonia (SMR = 26.5 in Israel [Kridin et al., 2017b]; SMR = 3.6 in

Taiwan [Huang et al., 2012]) and septicemia (SMR = 8.6 in Israel [Kridin et al., 2017b]; SMR = 11.6 in Taiwan [Huang et al., 2012]). Cardiovascular diseases, peptic ulcer disease, and malignancies additionally conferred an elevated risk of death (Huang et al., 2012; Jelti et al., 2019; Kridin et al., 2017b).

Comorbidities

Several controlled observational studies pointed to the coexistence of pemphigus with other autoimmune conditions. Leshem et al. (2011) and Parameswaran et al. (2015) found that rheumatoid arthritis and autoimmune thyroid diseases were significantly more prevalent in patients with pemphigus than in their first-degree relatives and the general population, respectively. The latter additionally depicted an association between pemphigus and type 1 diabetes mellitus (Parameswaran et al., 2015). In a recent retrospective cohort study, patients with pemphigus were found to be at a 2.5-fold increased risk of developing rheumatoid arthritis (Kridin et al., 2020a). Additional comorbidity was identified with Sjögren syndrome, systemic lupus erythematosus, and alopecia areata in a large-scale Taiwanese case-control study (Chiu et al., 2017). Ulcerative colitis, but not Crohn disease, was found to associate with pemphigus (Kridin et al., 2018b, 2017c). Even more intriguingly, first-degree family members of patients with pemphigus demonstrated a significant increase in the prevalence of autoimmune diseases when compared with controls (Firooz et al., 1994).

A compelling body of evidence recently accumulated to attest an association between pemphigus and psoriasis (Chiu et al., 2017; Hsu et al., 2016b; Kridin et al., 2017d). Data from these studies were synthesized in a meta-analysis, which revealed that the pooled multivariate OR for psoriasis in patients with pemphigus was significantly increased and estimated at 3.5 (95% CI = 1.6−7.6) (Kridin et al., 2019b). The overall pooled prevalence of psoriasis among patients with pemphigus was 2.4% (95% CI = 1.0−4.4) across all eligible studies (Kridin et al., 2019b).

The association of PV and PF with comorbid malignancies remains to be decisively established. In a Japanese study following 496 patients with pemphigus, the prevalence of internal malignancies (5.0%) was higher than expected in the general Japanese population (0.6%), with lung cancer being the most common solid malignancy. In a German cross-sectional study, PV was associated with gastrointestinal (OR = 2.6; 95% CI = 1.9−3.5), colon (OR = 2.4; 95% CI = 1.6−3.6), and oropharyngeal (OR = 7.2; 95% CI = 2.7−19.9) neoplasms, whereas PF was associated with non-melanoma skin cancer (OR = 2.5; 95% CI = 1.4−4.0) (Schulze et al., 2015). Patients with pemphigus from Israel were found to experience a higher burden of esophageal (OR = 2.9; 95% CI = 1.1−7.4) and laryngeal (OR = 2.0; 95% CI = 1.0−4.1) cancers as demonstrated by a population-based cross-sectional study (Kridin et al., 2018d).

The same Israeli dataset revealed an increased burden of chronic leukemia (OR = 2.1; 95% CI = 1.2−3.6), multiple myeloma (OR = 2.2; 95% CI = 1.2−3.9), and non-Hodgkin lymphoma (OR = 1.5; 95% CI = 1.0−2.2) in patients with pemphigus as compared with controls (Kridin et al., 2018c). This finding was further corroborated by Schulze et al. (2015), who showed a significant association of PV, but not PF, with hematologic malignancies (OR = 2.1; 95% CI = 1.4−3.0). Because these epidemiological observations may mirror an adverse event of mutagenic immunosuppressive agents utilized to manage pemphigus, two studies (Kridin et al., 2018c, 2018d) adjusted for exposure to these drugs. The significant association of pemphigus with esophageal (adjusted OR = 3.8; 95% CI = 1.2−12.3) and laryngeal (adjusted OR = 2.1; 95% CI = 1.0−4.3) cancer and chronic leukemia (adjusted OR = 2.0; 95% CI = 1.1−3.7) persisted, whereas the associations with multiple myeloma and non-Hodgkin lymphoma fell short of significance (Kridin et al., 2018c, 2018d). Although mutagenic immunosuppressants exert a substantial role in underlying the associations with multiple myeloma and non-Hodgkin lymphoma, further mechanisms are responsible for the associations with other malignancies.

Two recent Israeli cross-sectional studies, encompassing 1,985 patients and 9,874 controls, revealed an association of pemphigus with bipolar disorder (OR = 1.7; 95% CI = 1.0−2.9) (Kridin et al., 2018e) and schizophrenia (OR = 1.5; 95% CI = 1.1−2.2) (Kridin et al., 2019c). A smaller Israeli study has shown an increased prevalence of comorbid depression among patients with pemphigus relative to matched control subjects (OR = 1.19; 95% CI = 1.1−1.3) (Wohl et al., 2015). Anxiety and depression have been reported to correlate with disease activity (Tabolli et al., 2008) and to persist during quiescent periods (Tabolli et al., 2014). A large-scale population-based cross-sectional study disclosed an association of pemphigus with several neurological conditions, namely dementia (OR = 2.0; 95% CI = 1.8−2.2), epilepsy (OR = 1.8; 95% CI = 1.4−2.3), and Parkinson disease (OR = 2.1; 95% CI = 1.7−2.5) (Kridin et al., 2018f). The association of pemphigus with Parkinson disease and epilepsy was demonstrated in an earlier cross-sectional study (Hsu et al., 2016b).

An increased prevalence of osteoporosis was identified in patients with pemphigus as compared with control subjects (OR = 9.8; 95% CI = 6.3−15.1) (Wohl et al., 2010). Although it is tempting to assume that this condition arises from prolonged corticosteroid exposure, the significant association was robust to a multivariate analysis adjusting for this treatment (adjusted OR = 4.3; 95% CI = 2.4−7.5). This association was reproduced in subsequent observational studies (Hsu et al., 2016b; Tee et al., 2012).

Table 2 summarizes the well-established comorbidities found to be associated with pemphigus.

Genetics

In parallel with decreasing sequencing costs, an increasing number of studies based on genome-wide association analyses and selected genetic markers has been published in PV and PF, which were reviewed in Petzl-Erler (2020) and Vodo et al. (2018). *DRB1*0402* and *DQB1*0503* have appeared as risk alleles for PV in all study populations, as reviewed in Vodo et al. (2018). In fact, a great majority of patients with PV express one of the two alleles. In a meta-analysis of 18 studies on the association of PV with alleles of the HLA-DRB1 gene, *DRB1*04*, *DRB1*08*, and *DRB1*14* were significantly increased, and *DRB1*03*, *DRB1*07*, and *DRB1*15* were significantly decreased (Yan et al., 2012). In Chinese patients

Table 2. Associated Diseases in PV and PF

Associated Disease[1]	Population	Number of Pemphigus/ Control Patients	Outcome Measure
Autoimmune diseases			
Rheumatoid arthritis (Kridin et al., 2020a; Leshem et al., 2011; Parameswaran et al., 2015)	Israel	110/969[2]	$P = 0.016$
	United States	Not detailed	2.82 (1.33–6.00)[3]
	Israel	1,985/9,874	2.54 (1.31–4.92)[4]
Autoimmune thyroid disease (Leshem et al., 2011; Parameswaran et al., 2015)	Israel	110/969[2]	$P = 0.046$
	United States	Not detailed	6.03 (3.53–10.31)[3]
Diabetes mellitus type I (Parameswaran et al., 2015)	United States	Not detailed	5.07 (1.07–23.98)[3]
Myasthenia gravis (Hsu et al., 2016b)	United States	6,406/ca. 17.4 million	6.92 (2.55–18.79)[3]
Systemic lupus erythematosus (Chiu et al., 2017)	Taiwan	1,998/7,992	4.46 (1.88–10.6)[3]
Sjögren syndrome (Chiu et al., 2017)	Taiwan	1,998/7,992	15.0 (3.16–71.5)[3,5]
Alopecia areata (Chiu et al., 2017)	Taiwan	1,998/7,992	2.68 (1.26–5.67)[3,5]
Malignancies			
Leukemia (Hsu et al., 2016b; Kridin et al., 2018c)	United States	6,406/ca. 17.4 million	1.56 (1.08–2.24)[3]
	Israel	1,985/9,874	2.1 (1.2–3.6)[3,6]
Non-Hodgkin lymphoma (Hsu et al., 2016b; Kridin et al., 2018c)	United States	6,406/ca. 17.4 million	1.52 (1.15–2.03)[3]
	Israel	1,985/9,874	1.5 (1.0–2.2)[3]
Hematological malignancies (Schulze et al., 2015)	Germany	PV only: 860/5,142	2.10 (1.40–3.03)[3]
Multiple myeloma (Kridin et al., 2018c)	Israel	1,985/9,874	2.2 (1.2–3.9)[3]
Esophageal cancer (Kridin et al., 2018d)	Israel	1,985/9,874	2.9 (1.1–7.4)[3]
Laryngeal cancer (Kridin et al., 2018d)	Israel	1,985/9,874	2.0 (1.0–4.1)[3]
Oropharyngeal cancer (Schulze et al., 2015)	Germany	PV only: 860/5,142	7.21 (2.68–19.9)[3]
Gastrointestinal cancer (Schulze et al., 2015)	Germany	PV only: 860/5,142	2.56 (1.85–3.46)[3]
Colon cancer (Schulze et al., 2015)	Germany	PV only: 860/5,142	2.44 (1.16–3.62)[3]
Nonmelanoma skin cancer (Schulze et al., 2015)	Germany	PF only: 103/588	2.45 (1.43–4.04)[3]
Chronic inflammatory diseases			
Psoriasis (Chiu et al., 2017; Hsu et al., 2016b; Kridin et al., 2019b, 2017d)[7]	Israel	1,985/9,874	2.84 (2.09–3.85)[3]
	Taiwan	1,998/7,992	7.18 (5.55–9.29)[3]
	United States	6,406/ca. 17.4 million	2.8 (2.0–3.9)[3]
Ulcerative colitis (Kridin et al., 2017c)	Israel	1,985/9,874	1.9 (1.1–3.3)[3]
Chronic obstructive pulmonary disease (Kridin et al., 2018a)	Israel	1,985/9,874	1.3 (1.2–1.5)[3]
Neuropsychiatric diseases			
Dementia (Kridin et al., 2018f)	Israel	1,985/9,874	1.97 (1.77–2.20)[3]
Epilepsy (Kridin et al., 2018f)	Israel	1,985/9,874	1.78 (1.36–2.33)[3]
Parkinson disease (Kridin et al., 2018f)	Israel	1,985/9,874	2.09 (1.74–2.51)[3]
Bipolar disorders (Kridin et al., 2018e)	Israel	1,985/9,874	1.7 (1.0–2.9)[3]
Schizophrenia (Kridin et al., 2019c)	Israel	1,985/9,874	1.5 (1.1–2.2)[3]
Others			
Diabetes (Heelan et al., 2015)	Canada	295/Canadian general population	2.20 (1.64–2.87)[8]
Hypothyroidism (Heelan et al., 2015)	Canada	295/Canadian general population	1.53 (1.08–2.10)[8]

Abbreviations: OD, odds ratio; PF, pemphigus foliaceus; PV, pemphigus vulgaris.
Adapted from (Schmidt et al., 2019).
[1]Only studies that reported a positive association are shown.
[2]First-degree relatives.
[3]OR (95% confidence interval).
[4]Hazard ratio (95% confidence interval).
[5]In females.
[6]Remains significant after adjustment for immunosuppressive therapy (2.0 [1.1–3.3]).[3]
[7]In meta-analysis of 12 studies with various designs including 12,238 patients, 5 studies showed a significant association with a total OD of 2.4 (1.0–4.4).[3]
[8]Age-standardized prevalence ratio (95% confidence interval).

with PV, *DRB1*14* (Gao et al., 2018; Zhang et al., 2019), *DQB1*0503* (Zhang et al., 2019), and *DRB1*04* (Zhang et al., 2019) were also identified as the most relevant risk alleles in two recent GWASs. So far, four non-HLA genes that have been replicated in another patient cohort with have been described to be associated with PV— *DSG3* encoding for the PV autoantigen DSG3, *TAP2* encoding for an adenosine triphosphate–binding cassette transporter involved in antigen presentation, *IL-6* encoding for the pleiotropic cytokine IL-6, and *ST18* (Gao et al., 2018; Sarig et al., 2012; Schmidt et al., 2019; Vodo et al., 2018). ST18 regulates apoptosis and inflammation, two processes of direct relevance to the pathogenesis of PV (Yang et al., 2008). *ST18* was found to be overexpressed in the skin of patients with PV

as compared with healthy individuals (Sarig et al., 2012). Variations in *ST18* are the only genetic markers in PV so far that have been associated with clinical characteristics, such as more severe disease and higher age at disease onset (Etesami et al., 2018). However, the concept of genetic markers within ST18 being relevant for PV susceptibility does not appear to be universal, because in the German and Chinese population, no association between ST18 and PV has been observed (Gao et al., 2018; Sarig et al., 2012; Yue et al., 2014).

In both sporadic and endemic (Brazilian) PF, the strongest association was found with HLA *DRB1* alleles (*04 and*14) and, recently, with *DQB1*05:03* in Chinese Han (Lombardi et al., 1999; Miyagawa et al., 1997; Moraes et al., 1997; Petzl-Erler, 2020; Sun et al., 2019).

Environmental factors

Drugs are a rare but well-recognized trigger factor of pemphigus. Sulfur-containing agents, so-called thiol drugs, such as penicillamine and the angiotensin-converting enzyme (ACE) inhibitor captopril, are the most frequently reported culprits (Ruocco and Pisani, 1982). Nonsulfhydryl ACE inhibitors, pyrazolone derivates, penicillin, and rifampicin have also been associated with the onset of pemphigus (Brenner and Goldberg, 2011). After intake of thiol drugs, the predominant pemphigus variant is PF, and remission occurs in about half of the patients. In contrast, only 15% of cases induced by nonthiol drugs showed spontaneous recovery; most of them were PV (Wolf et al., 1991).

Two controlled studies reported exposure to pesticides and metal vapor and history of smoking as risk factors for pemphigus (Bastuji-Garin et al., 2002; Brenner et al., 2001). In a recent systematic review, a protective role of smoking was found to be possible in pemphigus (Lai et al., 2018). The positive effect of nicotine, a cholinergic agonist, in pemphigus may be explained by the observation that cholinergic agonists are able to reduce PV IgG autoantibody-induced acantholysis in vitro (Grando and Dahl, 2000). Furthermore, stressful life events were reported in close temporal context with the onset of pemphigus (Morell-Dubois et al., 2008) and, in individual patients, burns, surgery, and exposure to UV light or ionizing radiation (Micali et al., 1998b; Ruocco and Pisani, 1982). Exposure to latter physical factors, certain drugs, pesticides, and metal vapor only account for a small percentage of pemphigus cases, and the main pemphigus-inducing environmental factors remain still to be discovered. Two observations unique to pemphigus, however, may allow gaining further insight in the transformation of genetically susceptible individuals to patients with pemphigus: endemic PF and finding autoantibodies in family members of patients with PV.

In endemic Brazilian PF, epitopes on the salivary protein LJM11 of *Lutzomyia longipalpis*, a sand fly that may also transmit leishmaniasis, was found to be cross-reactive with DSG1-related desmosomal cadherins (Peng et al., 2021; Qian et al., 2012). Of interest, anti-DSG1 antibodies can be detected in about half of the endemic population (Warren et al., 2000), and the clinical manifestation of PF lesions was associated with a switch of IgG1 to IgG4 anti-DSG1 antibodies and a change of the autoantibody specificity from the extracellular (EC)5 domain to the EC1 and EC2 domains of DSG1 (Culton et al., 2008; Li et al., 2003; Qaqish et al., 2009; Qian et al., 2009). At present, it is unclear whether a second trigger in addition to exposure to *L. longipalpis*–derived LJM11 is required to induce clinical disease.

In PV and sporadic PF, circulating pemphigus-specific autoantibodies have been found in about half of the first-degree relatives of patients with pemphigus (Ahmed et al., 1993; Bhol et al., 1994; Brandsen et al., 1997; Kavala et al., 2007; Kricheli et al., 2000; Mohimen et al., 1993; Torzecka et al., 2007, 2003). In the first-degree relatives, similar to patients with PV in remission, anti-DSG3 antibodies predominantly belong to the IgG1 subclass (Bhol et al., 1994; Kricheli et al., 2000; Torzecka et al., 2007). In contrast, in patients with active PV, autoantibodies are mainly of the IgG4 subclass (Funakoshi et al., 2012; Futei et al., 2001).

These data suggest that different environmental factors can induce a break of tolerance against DSG1 and/or DSG3 in pemphigus and that development of overt clinical disease in genetically susceptible individuals may even involve a multistep process that requires different trigger factors.

PNP

PNP was first described by Anhalt et al. (1991). The main target antigens are DSG3 and the plakin proteins envoplakin and periplakin (Khudhur et al., 2014; Schmidt et al., 2019). A severe stomatitis, which frequently involves the lips and tongue, and the associated neoplasm are the clinical hallmarks that occur in nearly all patients. Of note, in about 10% of patients, the neoplasm may only be detected during the course of the disease (Ohzono et al., 2015), most likely because the tumor could not be recognized during the initial tumor search. The most frequent associated neoplasms are lymphoproliferative disorder (mostly non-Hodgkin lymphoma and chronic lymphocytic leukemia) that develop in 70–80% of patients with PNP. Thymoma, malignant solid tumors (among others, sarcoma, adenocarcinoma, squamous cell carcinoma, and malignant melanoma), and Castleman tumors are found in the remaining cases (Anhalt et al., 1991; Joly et al., 2000; Leger et al., 2012; Lehman et al., 2015; Ohzono et al., 2015; Schmidt et al., 2019). In China and Southern Korea, the most frequent associated neoplasma is Castleman disease (Choi et al., 2012; Liu et al., 2008; Wang et al., 2004).

Bronchiolitis obliterans was found in 6% of European patients with PNP but in 20% of Japanese patients and 70% of the reported children with PNP and appeared to be more frequent with underlying Castleman disease (Leger et al., 2012; Mimouni et al., 2002; Nikolskaia et al., 2003; Ohzono et al., 2015; Wang et al., 2005). The occurrence of bronchiolitis obliterans was explained experimentally by the ectopic expression of DSG3 in the lung (Hata et al., 2013). The lung disease in this mucocutaneous autoimmune blistering disorder led some authors to use the term paraneoplastic autoimmune multiorgan syndrome instead of PNP (Amber et al., 2018). In Chinese patients with PNP, an association with myasthenia gravis was reported in a third of patients (Wang et al., 2015).

Table 3. Age and Gender of Patients with Paraneoplastic Pemphigus

Origin[1]	Number of Patients	Female-to-Male Ratio	Mean Age ± SD (y)	Age Range (y)	Minors, %	≤30 Years of Age, %
United States (Anhalt et al., 1991)	5	1.5:1	58 ± 8	45–67	0	0
United States and/or Japan (Ohyama et al., 2001)	21	0.91:1	51 ± 15	17–70	5	10
United States[2] (Nikolskaia et al., 2003)	28	0.65:1	27 ± 20	8–68	50	64
China[2] (Wang et al., 2005)	10	1.5:1	27 ± 13	17–48	20	70
China (Zhu and Zhang, 2007)	17	0.7.1	35 ± 13	17–56	12	41
Germany (Zimmermann et al., 2010)	4	1:1	54 ± 15	31–65	0	0
Korea (Choi et al., 2012)	12	0.71:1	45 ± 13	19–67	0	8
France (Leger et al., 2012)	53	0.71:1	59[3]	30–88	0	2
Japan (Ohzono et al., 2015)	104	1.74:1	57 ± n.r.	11–83	n.r.	n.r.
France (Jelti et al., 2019)	12	2:1	71 ± 11	n.r.	0	0
Summary	266	1.09:1	51[4]	8–88	12	22

Abbreviation: n.r., not reported.
[1]Selected case series.
[2]Associated with Castleman disease.
[3]Median.
[4]Calculating median as mean.

The average age at the time of diagnosis is about 50 years, with Chinese patients being considerably younger, presenting at the age of about 30 years (Table 3). The latter observation may be due to the relatively frequent association of Castleman disease in children and the aforementioned high frequency of this neoplasm in Chinese patients with PNP (Liu et al., 2008; Mimouni et al., 2002; Nikolskaia et al., 2003; Wang et al., 2004). PNP affects both sexes nearly equally, with a female-to-male ratio of 1.09:1 (Table 3).

Based on HLA genotyping of 13 French and 19 Han Chinese patients compared with 152 and 562 control subjects, respectively, an association with *DRB1*03* and *Cw*14* was observed, respectively (Liu et al., 2008; Martel et al., 2003).

The prognosis of PNP is usually poor, with a mortality rate ranging from 75% to 90% (Schmidt et al., 2019). Its prognosis has been recently re-evaluated in large series of 53 patients whose 1-, 2-, and 5-year overall survival rates were 49%, 41%, and 38%, respectively (Leger et al., 2012). Infections and evolution of the neoplasm were identified as the main cause of death, with erythema multiforme-like skin lesions being associated with a two-fold increased risk of death following multivariant analysis (Leger et al., 2012). In patients with bronchiolitis obliterans and Castleman disease and patients below 30 years of age, mortality is greatly increased, with the lung disease being the main cause of death (Nikolskaia et al., 2003; Wang et al., 2005).

Impact of COVID-19

The management of pemphigus is challenging and often necessitates the administration of high-dose systemic corticosteroids and immunosuppressive agents (Kridin et al., 2019a). Treatment of this disease poses even a harder challenge in light of the COVID-19 pandemic, given the concern about the vulnerability of pharmacologically immunosuppressed patients. Therefore, the dermatological society struggles with a huge uncertainty regarding the optimal way to manage patients with pemphigus during the pandemic. Because severe COVID-19 is associated with a hyperinflammatory state termed cytokine storm (Shi et al., 2020; Vabret et al., 2020), it is of great interest to investigate whether the presence of preexisting autoimmune diseases or the previous use of immunosuppressive agents affects the phenotype of COVID-19. Data in this regard are conflicting; although certain studies demonstrated an increased risk and more aggressive course of severe acute respiratory syndrome coronavirus 2 infection in patients with autoimmune diseases (D'Silva et al., 2020; Gianfrancesco et al., 2020; Pablos et al., 2020), most others refuted this finding (Ansarin et al., 2020; Emmi et al., 2020; Fredi et al., 2020; Liu et al., 2020; Macaluso and Orlando, 2020). Recent expert recommendations have proposed guidance for the management of patients with pemphigus during the COVID-19 pandemic (Kasperkiewicz et al., 2020; Shakshouk et al., 2020). Very recently, by 14 January 2021, the task force on autoimmune bullous disease (AIBD) of the European Academy of Dermatology and Venereology (EADV) has recommended vaccination by the EMA-approved vaccines in Europe. Vaccinations should preferably be given when (i) AIBD is in a quiet phase; (ii) before immunosuppression is initiated; and (iii) not within the first three months after rituximab infusion, based on preliminary observations by Mahmoudi et al. (2020) (https://eadv.org/covid-19/task-force).

The same recommendations advocate including patients with pemphigus with COVID-19 in the online registry initiated by the EADV task force and hosted in Groningen, The Netherlands (https://recovab.umcg.nl). This registry is open to every physician worldwide and aims to gather epidemiological data about infected patients, determine whether certain medications or comorbidities are associated with the infection, and record the severity of COVID-19. These data will be valuable in estimating the risk of patients with pemphigus for COVID-19.

The burden of COVID-19 among patients with pemphigus is yet to be thoroughly investigated. In a population-based cohort study including 1,236 Israeli patients with

pemphigus, the risk of COVID-19 infection (hazard ratio [HR] = 0.81; 95% CI = 0.44–1.49), COVID-19–associated hospitalization (HR = 1.41; 95% CI = 0.53–3.76), and COVID-19–associated mortality (HR = 1.33; 95% CI = 0.15–11.92) was comparable in patients with pemphigus and their controls. Systemic corticosteroids and immunosuppressants did not seem to predispose COVID-19–positive patients with pemphigus to a more severe phenotype of COVID-19 (Kridin et al., in press). In a systematic review summarizing 732 reported patients with AIBD, of whom 211 had pemphigus, 16 patients (2.1%) had a confirmed diagnosis of COVID-19. Six patients (0.8%) had severe symptoms requiring hospitalization, and three patients (0.4%) died of COVID-19. This analysis, however, pooled patients with AIBDs together without differentiating between those with pemphigus and pemphigoid diseases (Kasperkiewicz, 2021). In an Iranian retrospective cohort study following 704 patients with AIBD, 21 patients (3.0%) tested positive for COVID-19, 15 patients (2.1%) were hospitalized, and 3 patients (0.4%) expired (Mahmoudi et al., 2020). Prednisolone >10 mg/day was associated with an increased risk of infection and COVID-19–associated hospitalization. The risk of these outcomes decreased notably as time from last dose of rituximab went by (Mahmoudi et al., 2020). Further research is warranted to estimate the outcomes of COVID-19 in patients with pemphigus originating from different backgrounds (Kasperkiewicz et al., 2020; Shakshouk et al., 2020).

Perspectives

Prevalence and incidence. All epidemiological data about pemphigus have been retrieved from retrospective studies using the medical records of one or more specialized tertiary centers or databases constructed to store health data either by national or private institutions. These approaches have considerable limitations. Retrospective studies by specialized tertiary centers have a selection bias for patients with more severe disease and patients who are more mobile and/or motivated to cover longer distances for treatment.

Data from national or private health provider and/or insurance databases are usually selected on the basis of International Classification of Diseases (ICD)-9 or ICD-10 codes. ICD coding is prone to multiple errors, including typographical errors, knowledge gaps in the relatively complex nomenclature of AIBD, and, importantly, the lack to reproduce the criteria on which the diagnosis has been made (Hsu et al., 2016a). As such, when Hsu et al. (2016a) tried to confirm the ICD-9–based diagnosis of pemphigus derived from a United States hospital data warehouse by reviewing the individual patient charts, the majority of identified patients had no clinical or diagnostic information to support the diagnosis of pemphigus. To validate the quality of the ICD-10–based data retrieved from the database of the largest German insurance company, we verified the number of male patients being coded as pemphigoid gestationis (which was none) and of woman older than 50 years (which was 4.5%) (Hübner et al., 2020; Schulze et al., 2015). The high number of patients coded with L10.9, that is, Pemphigus diseases, not further specified accounting of 24% of the total pemphigus diagnoses in our dataset highlighted at least the lack of knowledge and/or accuracy of the coding personnel for this entity (Hübner et al., 2020). When the diagnosis of PV in a database for United Kingdom physicians in primary care was compared with the database for inpatients, the positive predictive value was only 59.5% (Persson et al., 2020).

To circumvent some of the shortcomings of the latter databases, for example, selection bias in specialized centers and the relatively poor, or at least difficult to control, ICD coding quality, in 2016, we established a prospective registry for all newly diagnosed patients with AIBD, including pemphigus, in the state of Schleswig-Holstein, Germany (van Beek et al., 2021). Schleswig-Holstein, with its 2.9 million inhabitants, is the northernmost German state bordering Denmark to the north and the North and Baltic Seas to the west and east, respectively. In this ideal geographic situation, all four hospitals with dermatological services serving this population participate in documenting all newly diagnosed patients with AIBD. In addition, all approximately 110 dermatologists in private practice in Schleswig-Holstein are contacted yearly to enquire about their newly diagnosed patients with AIBD and their clinical and immunopathological characteristics. In this setting, six patients with PV and five with PF have been diagnosed in 2016, resulting in an estimated incidence of pemphigus in 3.8 per million inhabitants (van Beek N, personal communication). Because only very few (if any) patients with AIBD will be exclusively managed in primary care, this figure most likely represents the true incidence of pemphigus in Northern Germany. We anticipate that this registry will provide relevant longitudinal data and valuable information about comorbidities and mortality.

Mortality. Changes in mortality rates in pemphigus throughout the years reflected advances in therapeutic options for the disease. The major turning point in the prognosis of pemphigus is the advent of systemic corticosteroids. This historical discovery imparted a transformational improvement in the prognosis of pemphigus and decreased the mortality rates from 70% to 30% (Bystryn and Steinman, 1996). From this point on, clinicians were able to induce clinical remission and control the activity of pemphigus, thus turning pemphigus from a lethal disease to a manageable chronic disease. However, prolonged systemic corticosteroid treatment is typified by a wide array of multisystemic adverse events, thus imposing high burden of morbidity, and even mortality, on patients with pemphigus. For instance, patients with pemphigus experience an increased mortality because of cardiovascular diseases and peptic ulcer disease, which are known to emerge after prolonged corticosteroid administration (Huang et al., 2012; Jelti et al., 2019; Kridin et al., 2017b).

The subsequent increase in the therapeutic arsenal by utilization of corticosteroid-sparing immunosuppressants resulted in an additional drop in the mortality rates to 5% (Bystryn and Steinman, 1996; Risser et al., 2009; Uzun et al., 2006). This observation apparently originated from the fact that adjuvant agents facilitated faster tapering and a lower cumulative dose of systemic corticosteroids, thus reducing their potentially life-threatening adverse events (Kridin, 2018). In the landmark randomized controlled trial of Joly et al. (2017), rituximab, in conjunction with a low-dose short course of

prednisone, was compared with high-dose and long-term prednisone as a monotherapy. Participants in the first arm displayed a better safety profile and a lower incidence of grade 3−4 adverse events (Joly et al., 2017). Given its relatively low follow-up time, the study was statistically underpowered to reveal a significant difference in mortality. However, it represents a high-evidence proof of adjuvant drugs' utility in minimizing the devastating adverse events of long-term systemic corticosteroids.

Despite the favorable corticosteroid-sparing effect of adjuvant immunosuppressants, increased risk of infections remains a matter of concern (Ren et al., 2018). These drugs induce generalized impairment of the immune system physiologic function, rendering patients susceptible to infections (Desai et al., 2017), which were evidenced as the main cause of mortality among patients with pemphigus nowadays (Huang et al., 2012; Kridin et al., 2017b). Development of more targeted therapies, specifically eliminating autoreactive B and T cells, holds great promise to reduce the risk of infections and infection-associated mortality in pemphigus. Utilization of modified chimeric antigen receptor therapy to target DSG3-specific B cells was recently suggested. Human T cells were engineered so that they are able to express a chimeric autoantibody receptor (CAAR), including DSG3. In a murine experimental model, DSG3 CAAR T cells specifically eliminated DSG3-specific B cells in vivo and exerted a specific cytotoxic effect against B cells expressing anti-DSG3 B-cell receptors in vitro. This highly auspicious technology is expected to deplete DSG3-specific short-lived plasma cells and to reduce anti-DSG3 memory B cells, directly and indirectly, without inducing general immunosuppression (Ellebrecht et al., 2016).

Comorbidities. Investigating comorbidities between uncommon diseases was long considered a methodologically complicated task. Given the rare nature of pemphigus and the low number of patients available for studies, the comorbidity profile of these patients was not elucidated until the emergence of large-scale computerized datasets. These studies provide an insightful perspective on the associations of pemphigus with other conditions, an aim that could not be fulfilled by hospital-based small cohorts. However, they are hampered by the absence of immunopathological and immunoserological validation of cases.

Delineating the comorbidity profile of patients with pemphigus is of great clinical implication because it raises the awareness of clinicians about disease trajectories and enables them to screen for comorbid conditions and diagnose them earlier. Early diagnosis is an essential prerequisite to guarantee better outcomes. Comprehension of illness trajectories is additionally helpful in predicting and guiding management and decision-making in patients with pemphigus and in setting realistic expectations and communicating with the patient about prognosis (Schell and O'Hare, 2013).

Genetic and environmental factors. Pemphigus appears as a unique model disease that allows further exploring of the role of environmental factors that may elicit the generation of autoantibodies and, subsequently, clinical disease in genetically susceptible individuals without the requirement of time-consuming longitudinal studies. The main genetic susceptibility is conveyed by certain, relatively common in the general population, HLA II alleles, such as *DRB1*0402* and *DQB1*0503*. However, only a very small minority of individuals with these relatively frequent risk alleles will develop pemphigus. This notion may be explained by the presence of yet to be unraveled additional susceptibility genes or by environmental triggering factors. In the latter respect, few data have been published aside from the salivary protein LJM11 of *L. longipalpis* in endemic Brazilian PF discussed previously. However, the presence of antidesmosomal antibodies in about half of the first-degree relatives of patients with PV indicates that the development of pemphigus requires multiple hits of the same triggering factor or different environmental factors that occur at different time points during this process.

Future approaches may take advantage of the high rate of antidesmosomal antibodies in relatives of patients with PV and explore potential trigger factors, such as the skin or gut microbiome or exposure to pesticides. In addition, more sophisticated genetic analyses including exome and whole-genome sequencing of patients with pemphigus and fine analysis of the very rare cases of familial pemphigus, may reveal additional susceptibility loci.

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CONFLICT OF INTEREST
The authors state no conflict of interest.

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