Spectrum of autoimmune bullous diseases seen at Chris Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital, South Africa

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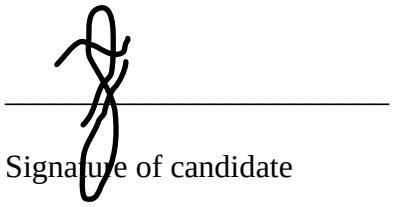
A research report (in the format of a "submissible" paper) submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree Master of Medicine (Dermatology)

Johannesburg, 2024

Declaration

I, Stephanie Adofo-Ansong, declare that this Research Report (in the format of a "submissible" paper) is my own, unaided work. It is being submitted for the Degree of Master of Medicine in Dermatology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



Signature of candidate

01 day of October 2024 in Johannesburg

Contribution of the Candidate to the Paper

Declaration: Student's contribution to the article and agreement of co-authors

I, Stephanie Adofo-Ansong, student number _1969082_, declare that this Research Report is my own work and that I contributed significantly towards the research findings presented in the paper intended for publication.

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Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her Research Report. In cases where the student is not the first author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for her degree purposes.

Article title: Spectrum of autoimmune bullous diseases seen at Chris Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital, South Africa

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Dedication

To Christ who gives me strength, and to my parents, without whom this would not have been possible, thank you for all the years of support and encouragement.

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Presentations arising from this body of work

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Stephanie Adofo-Ansong, Lindinkululeko Nkehli, Nombuyiselo Mvulane, Eunice van den Berg. Spectrum of autoimmune bullous diseases seen at Chris Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital, South Africa. Poster presentation. Wits Health Research Day. September 2024.

Future presentations

Stephanie Adofo-Ansong, Lindinkululeko Nkehli, Nombuyiselo Mvulane, Eunice van den Berg. Spectrum of autoimmune bullous diseases seen at Chris Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital, South Africa. Electronic poster display. 2025 American Academy of Dermatology Annual Meeting, United States of America. March 2025.

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List of Abbreviations

AIBDs	autoimmune bullous diseases
BP	bullous pemphigoid
BSLE	bullous systemic lupus erythematosus
DH	dermatitis herpetiformis
DIF	direct immunofluorescence
EBA	epidermolysis bullosa acquisita
IQR	interquartile range
LABD	linear IgA bullous dermatosis
LPP	lichen planus pemphigoides
MMP	mucous membrane pemphigoid
PE	pemphigus erythematosus
PF	pemphigus foliaceous
PG	pemphigoid gestationis
PNP	paraneoplastic pemphigus
PV	pemphigus vulgaris
PVe	pemphigus vegetans

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Abstract

Background Autoimmune bullous diseases (AIBDs) are potentially life-threatening blistering dermatoses in which autoantibodies target skin and mucous membranes. Epidemiologic data about AIBD subtypes are limited. We described the number of new cases of AIBDs at two academic hospitals in Johannesburg, South Africa, by demographics, AIBD subtype and year of diagnosis.

Methods We conducted a retrospective observational study of histopathology records from the laboratory database and patient demographic information from the hospital database. Eligible records included new diagnoses of AIBD confirmed between 2013 and 2021 by histology and direct immunofluorescence with or without salt-split skin testing. We collected data on demographics (age at diagnosis, sex and race), AIBD subtype and year of diagnosis. Descriptive statistics were calculated.

Results Over nine years, 169 people were newly diagnosed with AIBD, with a median age of 65 years. Most were female (66.9%) and Black African (91.1%). The commonest AIBD subtypes were bullous pemphigoid (68%), pemphigus foliaceous (9.5%), pemphigus vulgaris (7.7%) and linear IgA bullous dermatosis (7%). The median age at diagnosis and male-to-female ratios, respectively, for AIBD subtypes were 68 years and 1:2.3 (bullous pemphigoid), 55.5 years and 1:1 (pemphigus foliaceous), 46 years and 1:3.3 (pemphigus vulgaris) and 16 years and 1:0.7 (linear IgA bullous dermatosis). Per annum, there was a mean of 18.8 new AIBD cases.

Conclusion Few new AIBDs are diagnosed in Johannesburg, predominantly in older, Black African females. Subepidermal bullous disease, specifically bullous pemphigoid, is the most common AIBD, while pemphigus foliaceous is the predominant intraepidermal bullous disease.

Keywords Autoimmune bullous diseases, skin disease, vesiculobullous, pemphigoid, pemphigus, demography, South Africa

Conflicts of interest This study was supported by a research grant from the Dermatological Society of South Africa. Sponsors had no role in the study's design, manuscript preparation, or completion.

Introduction

A. Autoimmune bullous diseases (AIBDs) are chronic blistering dermatoses of the skin and mucosa that may be life-threatening if untreated.[1] AIBDs are characterised by the formation of autoantibodies targeting self-antigens in the skin and mucosa.[1]

B. AIBDs are broadly classified into two groups of diseases: subepidermal and intraepidermal bullous diseases. Each group has disease subtypes which differ in clinical presentation. Subepidermal bullous diseases are distinguished by injury to proteins at the basement membrane zone that result in clinically tense bullae and subepidermal blisters that are visualised histologically via light microscopy.[1,2] Tissue-bound autoantibodies are visualised using direct immunofluorescence (DIF) microscopy, and circulating autoantibodies are detected using indirect immunofluorescence microscopy, enzyme-linked immunosorbent assay, immunoblot or immunoprecipitation analyses.[1,2] Subepidermal bullous disease subtypes include linear IgA bullous dermatosis (LABD), epidermolysis bullosa acquisita (EBA), bullous systemic lupus erythematosus (BSLE), dermatitis herpetiformis (DH) and the pemphigoid disorders, which are bullous pemphigoid (BP), pemphigoid gestationis (PG), mucous membrane pemphigoid (MMP), lichen planus pemphigoides (LPP) and anti-p200 pemphigoid. LABD is also known as chronic bullous dermatoses of childhood in children.[1,2] When autoantibodies target desmosome proteins at epidermal cell-cell junctions, acantholysis occurs, leading to intraepidermal blisters and clinically flaccid bullae.[1,3] Intraepidermal bullous diseases or pemphigus disorders include pemphigus vulgaris (PV) and its variant pemphigus vegetans (PVe), pemphigus foliaceous (PF) and its variant pemphigus erythematosus (PE), paraneoplastic pemphigus (PNP), IgA pemphigus and pemphigus herpetiformis.[1,3]

C. AIBD groups vary geographically: subepidermal bullous diseases are more common in Western countries,[4–6] while intraepidermal bullous diseases are prevalent in Africa and Asia.[7–13] Globally, BP is the most common subepidermal bullous disease,[4,6–9,11–17] while PV is the most common intraepidermal bullous disease.[4,9,11–15] AIBDs can affect individuals of any age group. Worldwide, more females are affected.[5–9,11–14] There is racial and ethnic diversity. A few studies observed a rising incidence of BP in the West.[5,18]

D. Research on AIBD epidemiology is limited. Most studies worldwide and in South Africa have focused on one group of disorders. Studies describing the spectrum of AIBDs are scarce. This study outlines the AIBD spectrum in urban Johannesburg, South Africa, by clinical subtype, patient demographics, and number of new cases annually.

Materials and Methods

E. This was a hospital-based observational retrospective study.

F. The study setting was at two academic hospitals (Chris Hani Baragwaneth Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital) situated in Johannesburg, a city in South Africa's most populated province, Gauteng. In 2021, the Gauteng population of 15.8 million (26.3% of all South Africans) was 50% female, and 69.7% were older than 19 years.[19]

G. Demographic data was retrieved from the hospital administration databases and histopathology records from the National Health Laboratory Service database, which serves both hospitals.

H. We included all positive DIF results, with or without salt-split skin testing, that showed clinical and light microscopy features of AIBD. We excluded cases with clinical or histopathological features that were diagnostic of other dermatological

conditions. We also excluded duplicated or mismatched laboratory and hospital case numbers.

I. Between 01 January 2013 (when a new laboratory software program was installed) and 31 December 2021, we identified 667 electronic reports of DIF on skin biopsies from our hospitals. Of these, 314 cases were positive.

J. We used common clinical features, including skin and mucosal blisters, and histopathological features of AIBDs as detailed by Kasperkiewicz et al.[2] and Vassileva et al.[1] to make diagnoses. This minimised information bias resulting from using medical records. During histopathological analysis, intraepidermal blisters on light microscopy were classified as intraepidermal bullous disease and subepidermal blisters as subepidermal bullous disease. PV, PF and PNP are frequently observed intraepidermal bullous diseases in our hospitals, while BP, LABD, PG, EBA, LPP and BSLE are commonly seen subepidermal bullous diseases. A chicken wire IgG and/or C3 staining pattern on DIF defined an intraepidermal bullous disease. Upper epidermal staining diagnosed PF, lower epidermis, PV and epidermal and basement membrane zone, PNP or PE differentiated clinically.[1,2] Linear IgG and/or C3 staining at the basement membrane zone indicated BP, PG, EBA, LPP or BSLE depending on clinical presentation. Granular staining was also diagnostic for BSLE. Linear staining of IgA indicated LABD. Autoantibody staining on the roof of the blister differentiated BP, PG and LPP from other subepidermal bullous diseases on the floor on salt-split skin testing.[1,2] We diagnosed 169 AIBD cases.

K. We collated demographic data, including age, sex, and race.

L. Data were analysed using SPSS version 29 to generate descriptive statistics with counts and percentages and to calculate the annual frequencies of AIBDs. The Kolmogorov-Smirnov test assessed the normality of continuous variables. Non-

normally distributed variables, including age, were reported as the median and interquartile range (IQR). Statistical comparisons of means utilised the Mann-Whitney U test for two groups and the Kruskal-Wallis test for three or more groups. Categorical variables, including sex and race, were compared using the chi-square test or Fisher's exact test, as appropriate. P-values < 0.05 were considered significant.

M. This study was approved by the Human Research Ethics Committee (Medical), University of the Witwatersrand, South Africa (M220543).

Results

N. *Demographics*

O. Among individuals newly diagnosed with AIBD, the median age was 65 years (IQR 45-75), 113 (69.9%) were females, 56 (33.1%) were males, 154 (91.1%) were Black Africans (p<0.001), seven (4.1%) were Caucasians, four (2.4%) were Mixed-race individuals and four (2.4%) were Asians/Indians.

P. *Clinical subtypes*

Q. As shown in Table 1 and Fig. 1, most individuals newly diagnosed with AIBD had subepidermal bullous diseases (82.2%), specifically BP (68%), LABD (7%), PG (3%), EBA (3%), LPP (0.6%) and BSLE (0.6%).

R. About 17.8% of new AIBD cases were intraepidermal bullous diseases, specifically PF (9.5%), PV (7.7%) and PNP (0.6%). A few cases had rare variants of PF and PV, namely PE (two patients) and PVe (one patient), respectively.

S. Subepidermal bullous diseases

T. BP patients were elderly, with an average age of 68 years at presentation. Patients were more commonly females. Of those presenting with BP, there were 114 Africans, seven Caucasians, three Asians and two Mixed-race individuals. LABD patients were younger, with an average age at presentation of 16 years. There were equal

proportions of adults and children with LABD. The average age of the children was three years, and 29 years for the adults. The only group where males were predominant was in the LABD subgroup. Interestingly, LABD was more common in male children (male-to-female ratio of 1:0.2), whereas, in adults, females presented more commonly (male-to-female ratio of 1:2). All patients were African except one Mixed-race individual. EBA patients presented to us on average aged 47 years. They were frequently females, and all were African. PG patients were, on average, 21 years old. These females were Africans and presented in their second or third trimester of pregnancy, while one developed PG during the post-partum period. Only one middle-aged African male presented with BSLE, and one similarly aged African female with LPP.

U. Intraepidermal bullous diseases

V. Pemphigus patients were younger at presentation than BP patients. On average, PF and PV patients were 55.5 and 46 years old, respectively. PF patients had equal sex ratios, whereas a greater proportion of patients in the PV group were females, more than any other AIBD (male-to-female ratio of 1:3). However, there was no statistical significance (p=0.083). All PV and PF patients were African except one Asian patient who presented with PV. One Mixed-race patient aged 41 years had PNP.

W. *AIBD cases by year of diagnosis*

X. The lowest number of new AIBD cases was in 2013 (n=11), and the highest number was in 2017 (n=27) (Fig. 2). The mean number of new AIBD diagnoses was 18.8 per annum (SD 5). As depicted in Fig. 2, there were no significant increases in AIBD cases over the nine years (p=0.224).

Discussion

Y. As demonstrated in our research and other studies describing AIBD groups, there is a wide age range among those affected.[4,7–9,11–15] Similar to some global research,[5–9,11–14] we found that AIBDs have a female predominance (male-to-female ratio of 1:2), like many autoimmune disorders.[20] However, in China, males have a greater preponderance,[16] while in Greece, the sex ratio was almost equal but slightly higher for men.[15] The preponderance of Black African AIBD patients in our study (91.1%) is explained by the location of the two hospitals in the City of Johannesburg municipality, which has a majority Black African population (76.4%).[21]

Z. In our study, the most diagnosed AIBD group was subepidermal bullous disorders. This finding is consistent with reports from Senegal,[22] Switzerland and Germany.[4,6] However, it contrasts with reports in geographic locations where intraepidermal bullous disorders were the most common subtype: KwaZulu-Natal province in South Africa,[10] Tunisia,[13] Sudan,[12] Togo,[8] Kuwait,[14] Turkey (70% of AIBD patients),[11] Iran (80% of AIBD patients)[9] and Malaysia.[7] Environmental and genetic factors are thought to influence the prevalence of intraepidermal disorders in these areas.[3,13] We also found that BP was the most common subepidermal bullous disease subtype, similar to global data.[4,6–9,11–17] Autoimmune disorders typically affect younger and middle-aged people;[20] however, BP behaves differently. It is seen predominantly in older adults, with the incidence sharply increasing after age 75.[18] Higher incidences of BP in ageing Western populations have been linked to higher life expectancy,[18] while in developing African countries, lower incidences of BP may be explained by having a younger population.[8] Geographic variances may also result from differences in health-seeking behaviour, the underestimation of BP cases treated without histopathological confirmation, and the rising incidence of neurological conditions associated with BP in Western countries.[8,18]

AA. LABD was the next most common subepidermal bullous disorder and the fourth most common AIBD. It is seen in greater proportions in African countries and Kuwait[12–14,23] and less so in Western and Asian countries.[4,9,11,15–17] Africa's younger population may explain the disparity in LABD proportions compared to Western and Asian countries.[23] LABD typically affects preschool-aged children and adults between 40 and 60 years of age.[1] EBA and PG were seen at the same frequency. In most countries, EBA was less common than PG, except for Singapore, where EBA was the second most common subepidermal bullous disorder.[4,9,12–15,17] The higher proportion of EBA seen in our study, compared to other countries, may be explained by the finding that EBA is more frequent in Black patients and has a significant association with HLA-DRB1*15:03, especially in patients from Sub-Saharan Africa, highlighted in one study.[24] Surprisingly, no cases of EBA were described in the studies from Togo and Sudan, which are Sub-Saharan countries.[8,12] No cases of PG were recorded from Chinese and Singaporean studies,[16,17] both of which are similar in ethnicity, and Turkey and Uganda.[11,23] LPP and BSLE are both rare AIBDs. Among the nations reporting AIBD groups, a few cases of LPP were recorded in Kuwait (four),[14] in Sudan (one)[12] and a single case in our study. One case of BSLE was documented both in Sudan[12] and in our study. There were no cases of DH and MMP in our population.

BB. The average age of presentation of BP patients was 68 years, like in other African and Asian countries.[8,9,12,14] In European countries and some Asian countries, namely Singapore and Turkey, patients were much older, with an average age older than 70 years.[4–6,11,15,17] More females presented with BP in our study. This is comparable to most Asian and Western countries.[4–7,9,11,14,17] However, males predominated in other African countries and China.[8,12,13,16] Only in Greece was the sex ratio equal.[15] BP was the only AIBD seen in all races, and it was also the most

common. LABD was seen in younger patients at a median age of 16 years. Half of these patients were children, and the other half were young adults. Most of the children presented at an age of less than five years. This corresponds with data showing that chronic bullous dermatoses of childhood is the most common AIBD in children in KwaZulu-Natal, South Africa.[25] Males presented more frequently, comparable to Kuwait and Iran,[9,14] and in contrast to most countries.[11–13,15–17] All patients were African except for one Mixed-race patient. Our EBA patients had an average age of 47 years. They were predominantly female and all African. Five African female patients presented with PG at an average age of 21 years. PG patients in African and Asian countries are younger, between 20 and 30 years,[9,12,14] while those in Western countries and Tunisia are older than 30 years.[4,13,15] The youngest were from South Africa. This was expected as, in our country, the age group with the highest number of birth registrations is between 20 and 29 years.[26] In agreement with other studies, patients presented during the second or third trimester of pregnancy and one during the post-partum period.[4,13] We only saw one female African patient with LPP, aged 59 years and one male African patient with BSLE, aged 63 years.

CC. Intraepidermal bullous diseases were much less common than BP in our study. However, in a research letter detailing a record review of skin diseases treated at public hospitals in the eThekwini district of KwaZulu-Natal province, South Africa, intraepidermal bullous diseases or pemphigus disorders were the most common AIBD recorded.[10] The City of Johannesburg and eThekwini municipalities share similar age and sex distributions. Like Johannesburg, eThekwini has a majority black population (73.8%).[21] The predominant ethnic group is Zulu-speaking Black Africans, while in Gauteng, Black Africans of various ethnic backgrounds predominate and include Zulu, Xhosa, Sepedi, Sesotho, Setswana and Tsonga.[21] This highlights the wide

variation in the geographic and ethnic distribution of AIBDs. More patients presented with PF than PV in our study, making PF the second most common AIBD and PV the third most common. Our findings coincide with a research report conducted at Chris Hani Baragwanath Academic Hospital between 1987 and 1995, where more patients presented with PF than PV.[27] Likewise, a study conducted in KwaZulu-Natal, South Africa, between 1987 and 1999 showed that PF was the most common variant of pemphigus seen in Black Africans.[28] Interestingly, this study found PV more common in the Indian population. Out of our four Asian/Indian patients, only one had PV. The studies at Chris Hani Baragwanath Academic Hospital and in KwaZulu-Natal had similar ratios of PF to PV at 1.1 and 1.2, respectively, compared with our study at 1.2. Worldwide, PV is overwhelmingly the most common pemphigus disorder.[6,9,11–16] A high incidence of PV is seen in some ethnic groups, namely, Ashkenazi Jews, strongly associated with HLA-DRB1*04 and HLA-A*10, and those of Mediterranean origin.[3] PF dominates only in Tunisia, Mali, South Africa, Senegal, Brazil and other Latin American countries.[3,13,22,28,29] PF is reportedly more prevalent in Central and South Tunisia, especially among young women living in rural areas.[13] However, a more recent study in 2011 conducted in the North of Tunisia found PV to be the most frequent variant of pemphigus.[13] Endemic PF is known as Fogo Salvagem in Brazil. It is seen in young patients living in rural areas near rivers linked with the *Simulium* black fly.[3] PE is a rare variant of PF, which presents with clinical features of PF restricted to the face, resembling lupus or seborrheic dermatitis.[3] Finland is unique to other countries as PE is the most common form of pemphigus.[30] These findings highlight a more varied distribution of the different subtypes of pemphigus regarding geographic location and ethnicity than for pemphigoid disorders. They also emphasise the potential role of genetic and environmental factors in developing pemphigus. We

reported two cases of PE and one of PVe, a rare form of PV. PNP was uncommon in our population; only one case was recorded. It was not associated with malignancy at presentation. No cases of IgA pemphigus and pemphigus herpetiformis were documented in this study.

DD. Our pemphigus patients were older, over 50 years, than patients in the other South African, African and Asian studies who were over 40 years old.[8,9,12–14,16,22,28,29] In Kuwait, patients were very young, presenting at an average age of 36 years.[14] Our patients were similar in age to patients in Western countries and Turkey.[4,6,11,15,30] More females presented with pemphigus in our setting, much like most countries except Kuwait, Greece and China, where males predominated.[14–16] In our cohort, more females presented with PV than any other AIBD (male-to-female ratio of 1:3), although there was no statistical significance (p=0.083).

EE. A high proportion of BP cases were diagnosed in our study. There has been a rise in BP cases in France and the United Kingdom, which correlates closely with a growing life expectancy.[18] In South Africa, life expectancy increased between 2013 and 2021, from 63.5 to 64.8 years for males and 69.9 to 71.3 years for females.[19] However, despite an increasing life expectancy over time and a growing elderly population in Johannesburg,[19] there were no significant increases in AIBD cases over the nine years (p=0.224), particularly during the latter years. This may be explained by a dramatic increase in deaths between 01 July 2020 and 30 June 2021 during the COVID-19 pandemic[19].

FF. Our study's limitations include its retrospective design, which restricted control over data collection and may have introduced selection and information bias. Additionally, the number of AIBD cases seen at our hospitals is likely underestimated as only biopsied cases were included, while cases treated without histopathological

confirmation were not included. We also did not account for mucosal biopsies of cases seen by the ophthalmology and gastroenterology departments. The study did not control for comorbidities and treatment variables, which may have affected its outcomes. A larger-scale prospective study with an expanded sample size and an extended study period is recommended in our setting to establish causative relationships and trends.

Conclusion

GG. There are few new AIBD diagnoses per annum in urban Johannesburg, South Africa. Surprisingly, BP was the most common AIBD predominantly diagnosed in older, Black African females. Further research will elucidate whether BP cases are increasing in our country and if this may be attributed to a rising life expectancy similar to patterns observed in Western countries. PF was the most common intraepidermal bullous disease subtype, contrasting with the global data where PV prevails.

HH.

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Table 1 Demographic characteristics of patients diagnosed with autoimmune bullous diseases by subtype

AIBD	**n (%)**	**Median age at diagnosis in years (IQR)**	**Females (n)**	**Male (M): female (F) ratio**	**p-value**	**Black African race, n (%)**	**p-value**
Subepidermal bullous diseases	*139 (82.2)*	*65 (47-78)*	*94*	*1:2.1*	*<0.001*	*126 (81.8)*	*<0.001*
BP	115 (68.0)	68 (61-79)	80	1:2.3	<0.001	103 (66.9)	<0.001
LABD	12 (7.0)	16 (3-29)	5	1:0.7	0.564	11 (7.1)	0.004
EBA	5 (3.0)	47 (45-64)	3	1:1.5	0.655	5 (3.2)	0.025
PG	5 (3.0)	21 (19-32)	5	0:5.0	0.025	5 (3.2)	0.025
LPP	1 (0.6)	59	1	0:1.0	-	1 (0.6)	-
BSLE	1 (0.6)	63	0	1:0.0	-	1 (0.6)	-
Intraepidermal bullous diseases	*30 (17.8)*	*52.5 (39-68)*	*19*	*1:1.7*	*0.144*	*28 (18.2)*	*<0.001*
PF	16 (9.5)	55.5 (42-69.5)	8	1:1.0	1.000	16 (10.4)	<0.001
PV	13 (7.7)	46 (37-59)	10	1:3.3	0.083	12 (7.8)	0.002
PNP	1 (0.6)	41	1	0:1.0	-	0 (0.0)	-
Total	**169 (100.0)**	**65 (45-75)**	**113**	**1:2.0**		**154 (100.0)**	

AIBD, autoimmune bullous disease; n, number; IQR, interquartile range; BP, bullous pemphigoid; LABD, linear IgA bullous dermatosis; EBA, epidermolysis bullosa acquisita; PG, pemphigoid gestationis; LPP, lichen planus pemphigodes; BSLE, bullous systemic lupus erythematosus; PF, pemphigus foliaceous; PV, pemphigus vulgaris; PNP, paraneoplastic pemphigus

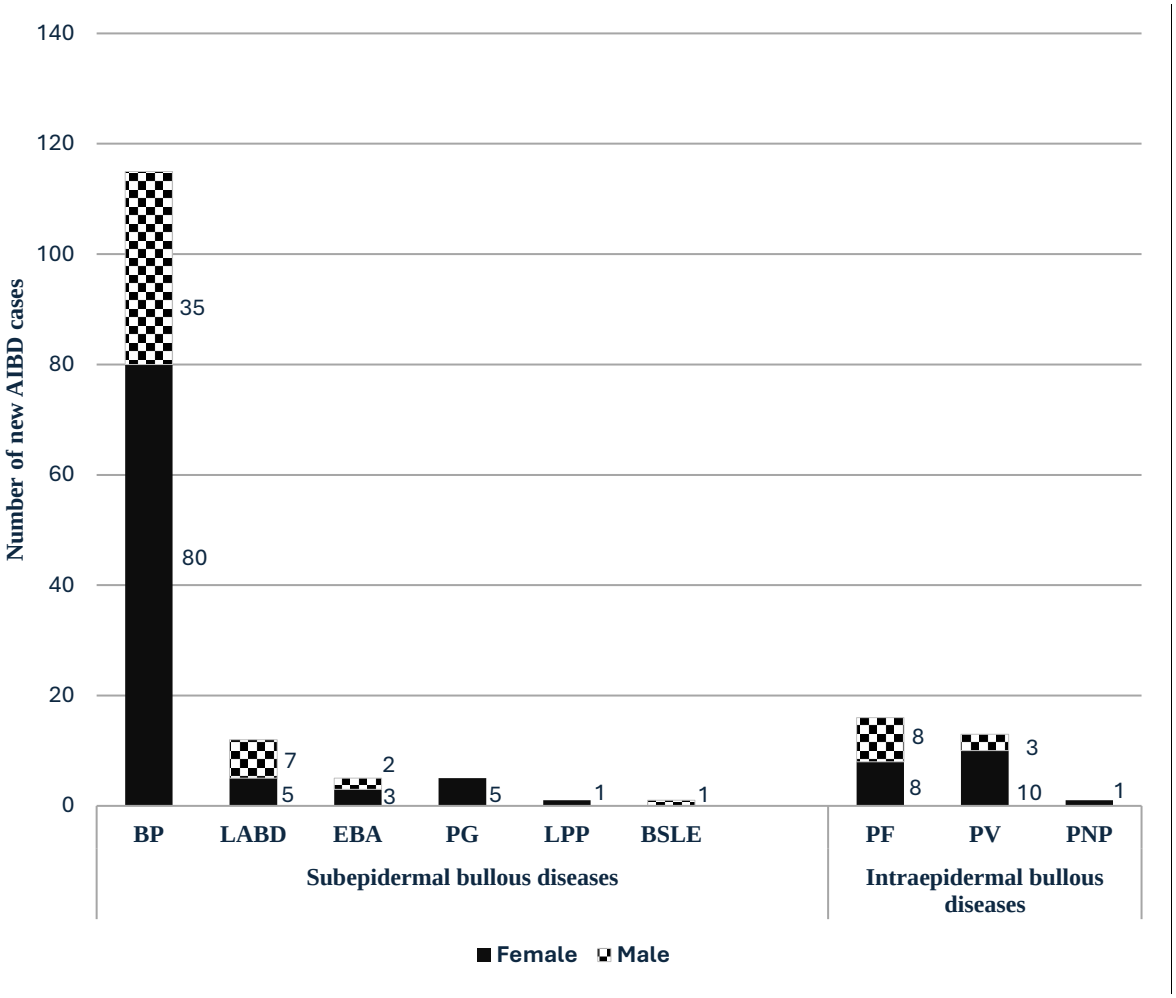

Figure 1 Number of autoimmune bullous diseases by sex

BP, bullous pemphigoid; LABD, linear IgA bullous dermatosis; EBA, epidermolysis bullosa acquisita; PG, pemphigoid gestationis; LPP, lichen planus pemphigoides; BSLE, bullous systemic lupus erythematosus; PF, pemphigus foliaceous; PV, pemphigus vulgaris; PNP, paraneoplastic pemphigus

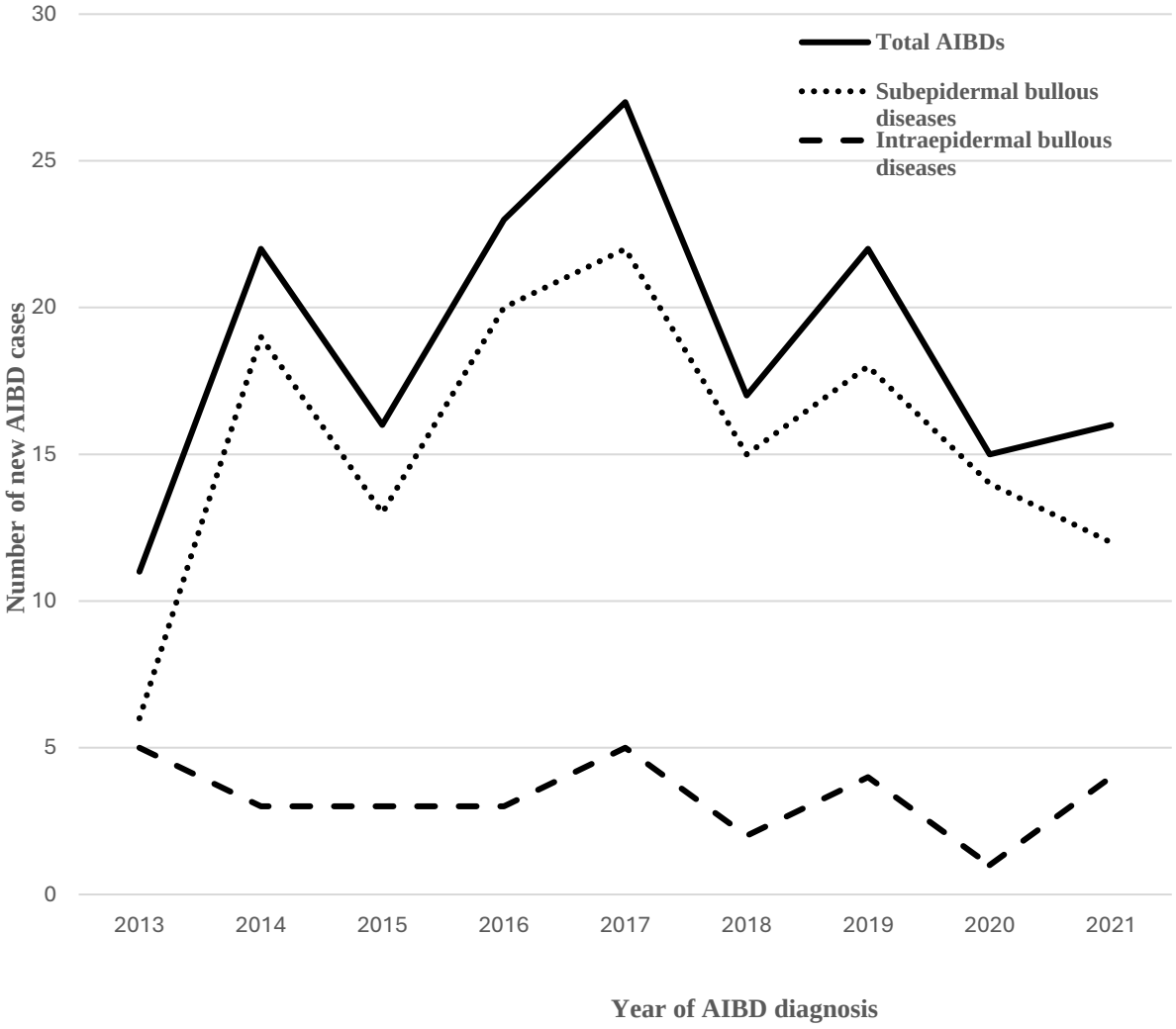

Figure 2 Number of new cases of autoimmune bullous diseases (AIBDs) by year of diagnosis

Appendix A: Approved research protocol

SPECTRUM OF AUTOIMMUNE BULLOUS DISEASES SEEN AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL AND CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL, SOUTH AFRICA

II. INTRODUCTION

JJ. Autoimmune bullous diseases (AIBDs) are a group of rare skin conditions characterised by the formation of blisters on the skin and mucous membranes, with a chronic clinical course (1). In a susceptible individual, the development of autoantibodies against adhesion molecules in the skin and mucous membranes results in the formation of a blister (2). Any age group may be affected, but some clinical subtypes are more common in certain age groups. For example, AIBDs such as bullous pemphigoid (BP) and linear IgA disease (LAD) are frequently seen in the elderly and children, respectively (3). Males and females are represented differently depending on the clinical subtype of the disease and their region of origin (4,5).

KK. Clinically, AIBDs may be visible as vesicles, bullae, erosions, excoriations or erythema on the skin and mucous membranes (3). More generalised lesions may result in significant fluid loss, electrolyte imbalance and increased risk of infection, making these diseases potentially life-threatening (3). Additionally, the chronic course and scarring associated with this disorder may lead to debilitating complications, such as blindness in some clinical subtypes, particularly mucous membrane pemphigoid (MMP), in which the ocular mucosa is significantly affected (5,6).

LL. AIBDs are classified as intraepidermal or subepidermal bullous diseases depending on the level of blister formation within the skin or mucous membrane or both histologically (1,3). Blisters that form within the epidermis of the skin are intraepidermal AIBDs, seen clinically as flaccid bullae. Blisters that form within the

basement membrane zone are subepidermal AIBDs that present as tense bullae (3,5). Pemphigus disorders make up the intraepidermal AIBDs and are characterised by autoantibodies targeted against desmosomal proteins that normally bind keratinocytes to each other (1,3). Several disorders make up the subepidermal AIBDs, including BP, and this group is characterised by the formation of autoantibodies directed against various protein molecules within the basement membrane zone (1,3).

MM. The diagnosis of AIBDs is based on clinical evaluation and histological examination. Furthermore, each clinical subtype may be distinguished by the type of autoantibody present and the specific antigen targeted through specialised investigations such as direct immunofluorescence (DIF), the salt-split skin test, immunoprecipitation, enzyme-linked immunosorbent assay and immunoblotting (5). Of these methods, DIF is considered the gold standard for diagnosing AIBD (3). The prognosis of AIBD patients has markedly improved through systemic corticosteroid therapy (2). However, its prolonged use is associated with adverse events resulting from immunosuppression such as diabetes mellitus, hypertension, cytopenia, osteoporosis, gastrointestinal ulcers and infections (2). Steroid-sparing immunosuppressants, including azathioprine, dapsone, doxycycline and mycophenolate, are usually added as a substitute to prevent these complications (3,5). Currently, the introduction of more targeted therapies such as rituximab and

intravenous immunoglobulins, which have fewer adverse effects, has shifted our focus away from broadly toxic immunosuppressive regimens (2,3,5).

NN. LITERATURE REVIEW

OO. Intraepidermal AIBDs

PP. *Clinical subtypes*

QQ. This group is made up of the pemphigus disorders. The main clinical subtypes include pemphigus vulgaris (PV), pemphigus foliaceous (PF) and paraneoplastic pemphigus (PNP), of which the earlier two have been most described (1). PV is further divided into a mucosal-dominant type and a mucocutaneous type (1). There are several variants of pemphigus that occur less commonly (1). Pemphigus vegetans is a variant of PV whereas, pemphigus erythematosus (PE) and endemic PF are variants of PF (7,8). Other variants of distinct clinical entities are pemphigus herpetiformis, drug-induced pemphigus and IgA pemphigus (1). Haematoxylin and eosin (H&E) and immunofluorescence studies differentiate between these clinical subtypes by highlighting the location of the blister within the epidermis and the different autoantibodies and antigens involved in disease pathogenesis. These are highlighted in Appendix B.

RR. Epidemiology

SS. The incidence of pemphigus differs widely between countries and among different ethnic groups (9). In Switzerland, for instance, the incidence of pemphigus was 0.6 cases per million between 2001 and 2002, while in Iran, the incidence was ten cases

per million between 1984 and 2003 (10,11). In a study conducted at Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg, the incidence was 0.14 per 100 000 between 1987 and 1995 (12). A spectrum study conducted in Iran showed an overall increase in the frequency of AIBDs between 1997 and 2006, and this trend was more pronounced for PV, which increased by 77% (13).

TT. Pemphigus was the most common disease in most regions reporting the spectrum of AIBDs (studies highlighted in Tables 1 to 3), including middle eastern countries like Kuwait, Turkey and Iran; African countries like Tunisia, Sudan and Toga; Malaysia in east Asia; and northern Greece (13-20). In these regions, the most frequent clinical subtype of pemphigus was PV. In Turkey and Iran, PV is so common that it outnumbers BP, the next most common AIBD, with a ratio of 5:1 and 8:1, respectively (13,16). Some pemphigus disorders occur more frequently in some ethnic groups. A study looking at the frequency of pemphigus disorders in Israel found a 3.6-fold higher likelihood of occurrence in Ashkenazi Jews than in the Arab population (21). This association has been linked to a genetic predilection for PV in the Jewish population carrying the PV-associated allele, HLA-DRB1*0402, more often (1). PF was a less common clinical subtype of pemphigus in most studies documenting the spectrum of AIBDs (13,16-19). However, in Tunisia, PF occurs more commonly than in other countries reporting the spectrum of AIBDs (20). This is because there is an

endemic focus of PF in Tunisia, and as in Brazil and northern Columbia, endemic PF occurs in rural areas (7).

UU. Unlike most countries, PF is the most common clinical subtype of pemphigus in Mali and KwaZulu-Natal (KZN), South Africa (22,23). Interestingly, the study by Bue looked at pemphigus in Johannesburg's black population between 1987 and 1995 and found a slightly increased frequency of PF than PV in this group, whereas a similar study from KZN between 1987 and 1999 found that PF occurs with a much greater frequency in the black population (12,22). PE is an uncommon variant of PF and was documented in Turkey and Iran as the least occurring variant (13,16). However, it is the most common variant of pemphigus in Finland (24). PNP is also a rare clinical subtype of pemphigus and only occurred in Iran and Sudan as the least occurring subtype (13,19).

VV. The average age of presentation for pemphigus was between the 4th and 6th decade across the spectrum studies (10,13-20). This was also observed in pemphigus studies conducted in KZN and Johannesburg in South Africa (12,22). In Kuwait, the average age of presentation was slightly younger, whereas western countries, such as Germany, Switzerland and the United Kingdom (UK), report a much older age of presentation (18,20,25,26). Regions with an endemic focus of PF differ in their average age of presentation. In Brazil, older children are affected; in Tunisia, young

adults are affected; and in northern Columbia, older people are affected between the third and sixth decade (7).

WW. In general, males and females have an equal representation of pemphigus. There was only a slight female predominance for pemphigus across the spectrum (13-16). This was also observed in South Africa (KZN), Finland and Israel (22,24,27). Female predominance was more pronounced in Mali, South Africa (Johannesburg), Tunisia and Sudan (12,19,20,23). In Kuwait and Greece, males predominated slightly (17,18). Furthermore, endemic PF affects the sexes differently. Males and females are equally affected in Brazil whereas, in northern Columbia, males and postmenopausal women are predominantly affected. In Tunisia, young females are affected (7).

XX. <u>Subepidermal AIBDs</u>

YY. *Clinical subtypes*

ZZ. The main forms of subepidermal AIBDs comprise BP, MMP, epidermolysis bullosa acquisita (EBA), pemphigoid gestationis (PG), LAD, anti-p200 pemphigoid, dermatitis herpetiformis (DH) and bullous systemic lupus erythematosus (BSLE) (1,28). These disorders differ widely in their overall clinical presentations, target antigens and autoantibodies. Hence, their treatment and prognosis differ, making their clinical distinction of fundamental importance (28). BP has a broad clinical range of presentations that may be localised or generalised (29). Localised variants are defined by typical BP lesions restricted to a specific anatomical location (29). Generalised

variants are distinguished by the type of skin lesions and their distribution. They include pemphigoid vegetans, erythrodermic BP, erosive or toxic epidermal necrosis-like BP, ecthyma-like BP and lichen planus pemphigoides (29). Finally, a variant of BP occurs in infants and children (infantile and childhood BP) that presents with lesions akin to adults (29). PG is a dermatosis of pregnancy occurring in one out of 40 000-50 000 pregnancies, particularly during the second and third trimester (30). There is an increased frequency of HLA-DR3, HLA-DR4 and HLA-C4 null alleles in these patients, and a woman may have antibodies directed against her partner's HLA antigens (5). DH is an AIBD associated with gluten-sensitive enteropathy, whereas, BSLE is an AIBD occurring specifically in patients with systemic lupus erythematosus (31).

AAA. *Epidemiology*

BBB. BP has a variable incidence rate depending on the geographic region. In the UK, the incidence was as high as 42.8 cases per million between 1996 and 2006, whereas, in Kuwait, the incidence was as low as 2.6 per million between 1991 and 2002 (9). It occurs most frequently within the subepidermal group and was the second most common AIBD after PV in the spectrum studies (10,13-20). However, in Germany, BP was the most common AIBD overall (10). Similar findings in other western countries such as Switzerland and the UK have been reported (25,26). This

may be because there is an increased prevalence of BP, a disease typically occurring in the elderly, in an increasingly ageing western population (9).

CCC. The other subepidermal AIBDs occur less frequently. PG is the next most frequently occurring across the spectrum studies and has a significantly higher prevalence in Kuwait than in other countries, including Iran, Germany and Tunisia (10,13,17,20). But, MMP and LAD occur more frequently than PG in northern Greece and Sudan, respectively (18,19). DH occurs in Malaysia, Germany, Tunisia, Sudan and Togo and has greater representation in Malaysia and Togo, where it is the third most common cause of AIBD (10,14,15,19,20). EBA was the least frequent subepidermal AIBD across the spectrum studies, and BSLE only occurred in Sudan as the least most common AIBD (10,13,17-20). Anti-p200 pemphigoid is very rare, such that it was not reported in any of the spectrum studies (1).

DDD. BP is a disease of the elderly and was generally seen between 60 and 80 years in the spectrum studies (10,13-20). In Iran, Malaysia, Tunisia and Togo, BP had a broader age range, affecting much younger people at the lower end of the range (13-15,20). In western countries, the age range is skewed towards a much older population, as was evident in northern Greece and Germany (10,18). A similar finding in Switzerland showed that the incidence of BP significantly rises with increasing age (26). PG is a disease of pregnancy shown to occur predominantly during the second and third trimesters in Tunisia and Germany (10,20). There was a younger age of

onset in Kuwait and Iran compared to Greece, Germany, Tunisia and Sudan (10,13,17-20). MMP generally presented in elderly patients between 60 and 80 years except in Iran, where it affected middle-aged people and one case in Sudan, which affected a child (10,13,16,18-20). LAD has a bimodal age of presentation, mainly affecting children and young adults in Kuwait, Sudan and Tunisia and affecting mostly adults in Iran, Turkey, Germany and northern Greece (10,13,16-20). LAD is reported more frequently in children in African countries (10). This was observed in Tunisia, Sudan, Mali, Uganda and South Africa (19,20,32-34). EBA had a varying age of presentation from 36 to 70 years (10,13,16-18,20). DH affects middle-aged adults in Germany and Sudan but affects younger adults in Malaysia, Tunisia and Togo, and it is reportedly rare after 30 years of age in Malaysia (10,14,15,19,20). Only one case of BSLE was seen in the study in Sudan, presenting at the age of 38 (19).

EEE. BP has a female predominance in most countries except for African countries such as Tunisia, Sudan and Togo, where males predominated (10,13-20). In Kuwait, the female predominance is greatly pronounced; BP is about six times more common in females (17). PG is a disease of pregnancy affecting females (30). MMP was generally more common in females, except in Tunisia, where all individuals identified were males (13,16,18-20). LAD was similarly widespread in females except in Kuwait and Iran, where males predominated (13,16-20). Likewise, for EBA, females presented more commonly except in Iran, where males were six times more likely to

present with EBA (13,16-18,20). Most patients presenting with DH were females; however, in Sudan, males were the predominant group (14,15,19,20). The only case of BSLE seen in the study in Sudan was a female (19).

FFF. JUSTIFICATION FOR THE STUDY

GGG. Very few studies worldwide have compared the spectrum of AIBDs as a whole, including intraepidermal and subepidermal AIBDs. Most have focused on a specific group of disorders or a disease entity. Likewise, in South Africa, several case studies on AIBDs have been published and few studies have compared the spectrum of AIBDs. So far, a study in KZN. has compared the frequency, demographics, clinical features and histopathology of the different pemphigus disorders (22). Similarly, a study in Johannesburg compared the frequency, demographics and histopathology of the pemphigus disorders (12). The proposed study will make a comprehensive comparison between the various clinical subtypes of AIBDs.

Table 1: Comparison of the frequency (%) of AIBDs between different countries									
Clinical subtype	Place/Frequency (%)								
	Kuwait (2004)[17]	Turkey (2021)[16]	Iran (2012)[13]	Malaysia (1992)[14]	Northern Greece (2017)[18]	Germany (2009)[10]	Tunisia (2011)[20]	Sudan (2021)[19]	Togo (2021)[15]
Pemphigus disorders	47			56.7			52.9		40.5
PV	39	70	81.2		42.8	2.4	33.9	50.9	
PF	8	7	4.4		5		19	8.2	
PE		1.4	0.1						
PNP			0.2					0.3	
Pemphigoid disorders									
BP	25	13	11.6	34.5	37.8	65.8	23.6	28.2	22.8
PG	19		0.7		2.5	9.8	10.3	1.4	
MMP		1.2	0.7		7.5	9.8	1.1	0.2	
LAD	7	4	0.4		2.5	4.9	6.3	8.4	
EBA	2.3	2	0.5		0.8	2.4	0.6		
Anti-p200									
Other AIBDs									
DH				8.8		4.9	5.2	0.9	13.9
BSLE								0.2	

Table 2: Comparison of the mean age (years) and range of AIBDs between different countries									
Clinical subtype	Place/Age (years)								
	Kuwait (2004)[17]	Turkey (2021)[16]	Iran (2012)[13]	Malaysia (1992)[14]	Northern Greece (2017)[18]	Germany (2009)[10]	Tunisia (2011)[20]	Sudan (2021)[19]	Togo (2021)[15]
Pemphigus disorders							50 (13-90)		43.7 (±19.4)
PV	36.53 (±11.08)	51.4	43.43 (±15.95)	30-60	56.7 (30-84)	62		40.4 (±15.3)	
PF	36.88 (±12.83)	49.4	42.2 (±17.41)		59.6 (29-84)			46.3 (±18)	
PNP			35.67 (±34.03)					51.5 (±13.4)	
Pemphigoid disorders									
BP	65.97 (±16.69)	75.6	59.41 (±19.57)	40-80	76.1 (55-90)	74.6	68.6 (15-102)	66 (±15.8)	60.6 (±24.7)
PG	28.61 (±6.01)		25.7 (±4.64)		36.3 (32-40)	33	31.7 (19-40)	29.5 (±9.7)	
MMP		67	45.5 (±19.37)		66.7 (48-83)	76.3	73.5 (70-77)	6	
LAD	12.66 (±17.02)	43.7	22.4 (±13.94)		51 (4-77)	31	18 (0.75-41)	9 (±11.8)	
EBA	59.07 (±9.09)	49.4	40.29 (±11.57)		70	36	53		
Anti-p200									
Other AIBDs									
DH				≤30		42.5	26 (4.5-66)	49.2 (±24.3)	25.6 (±25.3)
BSLE								38	

Table 3: Comparison of the male to female ratio (M: F) of AIBDs between different countries									
Clinical subtype	Place/M: F ratio								
	Kuwait (2004)[17]	Turkey (2021)[16]	Iran (2012)[13]	Malaysia (1992)[14]	Northern Greece (2017)[18]	Germany (2009)[10]	Tunisia (2011)[20]	Sudan (2021)[19]	Togo (2021)[15]
Pemphigus disorders				1:1			1:2		0.8:1
PV	1.4: 1	1:1.4	1:1.39		1.21:1	-		1:2.3	
PF	1:2.7	1:1.09	1:1.34		2:1			1:2.2	
PE		-	All F						
PNP			1:2					All M	
Pemphigoid disorders									
BP	1:5.75	1:1.25	1:1.36	1:1.17	1:1	1:1.2	1.56:1	1:0.9	1.2:1
PG	All F		All F		All F	All FA	All F	All F	
MMP		1:1	1:1.5		1:1.3	-	All M	All F	
LAD	1.7:1	1:1.6	1.5:1		1:2	-	1:1.75	1:1	
EBA	0:3	1:0.75	6:1		All F	-	All F		
Anti-p200									
Other AIBDs									
DH				0.6:1		-	1:2	1:0.3	0.8:1
BSLE								All F	
- (data not shared)									

STUDY AIM

To describe the spectrum of AIBDs and the demographics of the affected patients seen at Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

STUDY OBJECTIVES

1. To list the clinical subtypes of AIBDs seen at CHBAH and CMJAH in order of frequency of occurrence from 1st January 2013 to 31st December 2021
2. To describe the demographics of patients with the different clinical subtypes of AIBD seen at CHBAH and CMJAH during the study period
3. To analyse the trend in the frequency of occurrence for the AIBDs seen at CHBAH and CMJAH over the study period

METHODS

Study design

This is a retrospective observational study of all patients diagnosed with an AIBD, from the 1st of January 2013 to the 31st of December 2021, at two Johannesburg teaching hospitals. Patient histopathology records will be obtained from the National Health Laboratory Service (NHLS) located at Chris Hani Baragwanath Academic hospital (CHBAH) and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The diagnosis will be based on the histopathological findings of the patient's skin biopsies. They will be identified by searching the NHLS records via the Academic Affairs and Research Management System facility (AARMS). Demographic data will be obtained from NHLS records of filled request forms sent with skin biopsy samples. Also, hospital data on patient demographics from the administration department will be utilized.

Study population

The study population will be all the patients with a confirmed diagnosis of AIBD who were attended to at the CHBAH and CMJAH from the 1st January 2013 to the 31st of December 2021.

Inclusion criteria

Only skin biopsy samples with a confirmation of AIBD on H&E and DIF, with or without salt-split skin testing, will be included in the study.

Exclusion criteria

Skin biopsy samples of patients with suspected AIBD with inconclusive results on H&E and DIF with or without salt-split skin testing.

Site of study

The Johannesburg teaching hospitals, CHBAH and CMJAH, are tertiary hospitals offering specialised health services. They are connected to the University of the Witwatersrand Health Sciences Faculty and provide teaching to undergraduate and postgraduate trainees. The CHBAH is the third-largest hospital in the world, with a bed occupancy of 3200. It is situated in Soweto, Johannesburg (35). The CMJAH is located in Parktown, Johannesburg and has a bed occupancy of 1088 (36). The NHLS is the largest diagnostic pathology service in South Africa and serves 80% of the population. NHLS laboratories are located in all nine South African provinces (37).

Study tool

A data collection sheet will be used to capture patient demographics, including age, sex, race and histopathological findings in the format represented in Appendix A.

Study definitions

The clinical subtypes of AIBD are classified as: intraepidermal AIBDs made up of the pemphigus disorders; and the subepidermal AIBDs, including BP, MMP, EBA, PG, LAD, anti-p200 pemphigoid, DH and BSLE (1,28). They are mainly differentiated by their histopathological features. H&E and DIF will be used to distinguish the histopathological features in this study. Common H&E and DIF findings seen in each clinical subtype of AIBDs are represented in the table in Appendix B adapted from Kneisel and Hertl (30) and Vassileva et al. (31).

DATA ANALYSIS

Raw data will be collected on a Microsoft® Excel spreadsheet. Analysis of data will be conducted using SPSS Statistics. The AIBD subtypes will be summarised using frequencies and percentages. Continuous data such as age will be reported as a mean and standard deviation if data is normally distributed or as a median and interquartile range for non-normal data. When comparing the subtypes with a continuous variable, a T-test will be used for normal data or the Mann Whitney Test for non-normal data. When comparing the subtypes with categorical variables such as sex, the Chi-square test will be used.

ETHICS

Before starting the study, permission will be requested from the CEO or Medical Superintendent at CHBAH, CMJAH and the NHLS. Permission will also be requested from the heads of department of anatomical pathology and dermatology at the University of the Witwatersrand, CHBAH and CMJAH. Ethical clearance will be obtained from the medical branch of the University of Witwatersrand Human Research Ethics Committee. Patient details such as name, hospital number and skin biopsy specimen number will be left out of the research process to maintain anonymity and safeguard the patient's interest. In addition, the dataset will be secured on a password protected device.

TIMING

The study will commence in May 2022 with an expected duration of one year. The Gantt chart details deadlines for the parts of the study (Figure 1).

	2021		2022											
	Nov	Dec	Jan	Feb	Mar	Apr	May	June	July	Aug	Sep	Oct	Nov	Dec
Literature review														
Preparing protocol														
Protocol assessment														
Ethics application														
Collecting data														
Data analysis														
Writing up thesis														
Writing up paper														

Figure 1: Gantt chart for the proposed study

FUNDING

This is a self-funded study costing a total of R2000. The expenses are detailed in the table below (Figure 2).

Expense	**Cost**
Printing	R1500
Binding	R500
Total	R2000

Figure 2: Table of expenses

LIMITATIONS

Data obtained from the Gauteng NHLS database will represent the two Johannesburg teaching hospitals but may not reflect the Gauteng province or South Africa. Therefore, direct inferences cannot be made from this data. Some data may be missing due to the time-lapse,

and reporting bias cannot be excluded. The biopsy technique of past and present clinicians may affect the interpretation of biopsy specimens and limit the sample size and results.

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APPENDIX A

Data collection sheet: Spectrum of Autoimmune bullous diseases

General information

1. Case number/Unique ID

2. Year of presentation

Demographics

3. Age

4. Sex

- ☐ Male
- ☐ Female

5. Race

- ☐ African
- ☐ Caucasian
- ☐ Asian
- ☐ Mixed

Clinical involvement

6. Region involved

- ☐ Cutaneous
- ☐ Mucous membranes
- ☐ Nails
- ☐ Other
    - ➢ Specify: _____

Histopathological features

7. Location of blister

- ☐ Intraepidermal (Intracorneal)
- ☐ Intraepidermal (suprabasal)
- ☐ Subepidermal

8. Inflammatory cell present

- ☐ Yes
- ☐ No

9. Amount of inflammatory cell present

- ☐ Cell rich
- ☐ Cell poor
- ☐ None

10. Predominant inflammatory cell

- ☐ Neutrophils
- ☐ Eosinophils
- ☐ Lymphocytes
- ☐ Other
    - ➢ Specify: _____

11. Other characteristic features on histology

- ☐ Acantholysis
- ☐ Interface dermatitis
- ☐ Intra-papillary micro-abscesses
- ☐ Other
    - ➢ Specify: _____

12. Autoantibody/Immunoreactant present

- ☐ IgA
- ☐ IgG
- ☐ C3
- ☐ Other
    - ➢ Specify: _____

13. Staining pattern

- ☐ Linear staining along BMZ/DEJ
- ☐ Granular staining along BMZ/DEJ
- ☐ Granular staining in the tips of the dermal papillae
- ☐ Other
    - ➢ Specify: _____

Diagnosis

_____

APPENDIX B

Diagnostic characteristics of AIBDs				
Intraepidermal blistering disorders				
Diagnosis	**Clinical findings**	**Histology**	**DIF**	**Main Autoantigens**
Pemphigus vulgaris (PV)	Painful mucous membrane erosions, Fragile blisters, erosions, crusts Positive Nikolsky sign	Intraepidermal suprabasal acantholysis Occasional "tombstone" pattern	Intercellular IgG and C3	**Dsg 3** **Dsg 1** (Dsg 4) Acetylcholine receptor, Dsc1-3
Pemphigus foliaceous (PF)	Fragile blisters, puff pastry-like scale in seborrheic areas	Superficial subcorneal acantholysis	Intercellular IgG and C3	**Dsg1** (Dsg4) Plakins
Paraneoplastic pemphigus	Polymorphic features: haemorrhagic stomatitis, palmoplantar lichenoid exanthems, blisters favouring trunk, partly multiforme-like	Interface dermatitis, lichenoid infiltrate of the DEJ, keratinocyte necrosis	Intercellular IgG and C3 And IgG and C3 along the DEJ	Dsg 3 (IgG, IgA) Dsg I Desmoplakin I and II **Envoplakin, periplakin** (IgG, IgA)

IgA pemphigus	Intraepidermal neutrophilic dermatosis	Fragile blister, pustules, annular plaques with collarette-like scaling	Intraepdermal infiltration by neurtophils	Usually without classical acantholysis	Intercellular IgA and C3	**Dsg 1** (IgA) **Dsg 3** (IgA)
	Subcorneal pustular dermatosis		Subcorneal infiltration by neutrophils			**Dscl** (IgA)
Subepidermal blistering disorders						
Diagnosis		**Clinical findings**	**Histology**		**DIF**	**Main autoantigens**
Bullous pemphigoid (BP)		Pruritis, tense blisters, erosions, crusts Urticarial, prurigo-like or eczematous plaques	Subepidermal blistering cell-rich variety: marked inflammatory infiltrate (especially eosinophils)		Linear C3 and IgG along DEJ (IgM, IgA)	**BP 180** (BP 230)
Pemphigoid gestationis (PG)		Usually, periumbilical start Grouped in part, target-like plaques, vesicles, pruritis, erythemas	Subepidermal blistering tissue eosinophilia		Linear C3 along DEJ (IgG, IgA, IgM)	**BP 180** (BP230)
Mucous membrane pemphigoid (MMP)		Erosions, ulcerations, scarring, strictures, atrophy of mucous membrane symblepharon	Subepidermal blistering fibrosis during course		Linear IgG and C3 along DEJ (IgA, IgM)	**BP180** (IgG, IgA) **Laminin 332** (BP230) α6 integrin, β4 integrin

Linear IgA dermatosis (LAD)	Pearl necklace-like grouped blisters, annular lesions Mucous membrane involvement	Histology not diagnostic Subepidermal blisters Occasionally intrapapillary microabscesses	Linear IgA and C3 along DEJ	**LAD-1** (IgA) BP180 (IgA) BP230 (IgA)
Epidermolysis bullosa acquisita (EBA)	Mechanobullous variety with blisters at mechanically stressed sites Inflammatory and atrophic variety Mucous membrane involvement	Subepidermal blistering with neutrophilic infiltrate in the dermal papillae	Linear IgG, C3 (IgA) along the DEJ	**Collagen VII** (IgG, rarely IgA)
Anti-laminin γ1 pemphigoid	Erythematous plaques and tense blisters on the trunk	Subepidermal cleavage	Linear IgG and C3 along the DEJ	**Laminin γ1 chain**
Dermatitis herpetiformis (DH)	Burning pruritis, grouped excoriated papulovesicles with extensor surface and gluteal accentuation	Subepidermal blistering Papillary abscesses with neutrophils (pathognomonic)	Fine granular IgA and C3 focally in the tips of the papillae or granular-linear along the DEJ	**Epidermal transglutaminase** (cross reaction with tissue transglutaminase)
Bullous systemic lupus erythematosus (BSLE)	Meets diagnostic criteria for SLE Vesicles and bullae over sun-exposed skin	Histopathology compatible with DH	Linear or granular deposits of IgG and C3 at BMZ, rarely IgA and IgM	Type VII collagen

Appendix B: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Dr S Adofo-Ansong

School of Clinical Medicine
Department of Medicine
Division of Dermatology Medical School

University

E-mail: steph.a.a@hotmail.com

CC: Supervisor: Drs L Nkehli, N Mvulane and E van den Berg <tabszako@yahoo.co.uk>

and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr lain Burns

Human Research Ethics Committee (Medical) Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2022/09/05

REF: *R14/49*

PROTOCOL NO: M220543 (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Spectrum of autoimmune bulbous diseases seen at Chrl's Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital, South Africa*

Please find attached the Clearance Gertificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr S Adofo-Ansong

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M220543

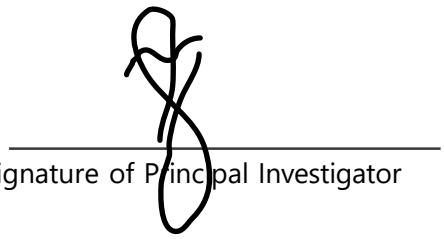
NAME: (Principal lnvestigator)	Dr S Adofo-Ansong
DEPARTMENT:	School of Clinical Medicine Department of Medicine Oivision of Dermatology Medical School University
PROJECT TITLE:	*Spectrum of autoimmune bulbous diseases seen at Chris Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital, South Africa*
DATE CONSIDERED:	2022/05/27
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen. Potgieter@wits.ac.za>
SUPERVISOR:	Drs L Nkehli, N Mvulane and E van den Berg
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/09/05

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and ONE COPY returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly eroqress reeort. When a funder requires annual re-certification, the application date will be one year after the date 'when the study was initially reviewed. In this case, the study was initially reviewed in May and therefore reports and re-certification will be due in the month of May each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).



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Signature of Principal Investigator Date

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Articles that relate to social, economic, cultural, artistic and humanitarian aspects of medicine. This contribution should not exceed 1200 words in length, with a maximum of 2 figures or tables and 5 references.

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1. de Berker DAR, Baran R, Dawber RPR. The Nail in Dermatological Diseases. In:*Baran and Dawber's Diseases of the Nails and their Management*(Baran R, Dawber RPR, de Berker DAR, Haneke E, Tosti, A, eds), 3rd edn. Oxford: Blackwell Science Ltd., 2001: 172–U2.
2. Murray ML, Cohen JB. Mycophenolate mofetil therapy for moderate to severe atopic dermatitis. *Clin Exp Dermatol* 2007; 32: 23–7.
3. Graham-Brown R, Burns T. *Lecture Notes: Dermatology*. Oxford: Wiley-Blackwell, 200S.
4. Smith A. (1UUU) Select committee report into social care in the community [WWW document]. URL http://www.dhss.gov.uk/reports/report015285.html [accessed on 7 November 2003].

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