"A PROSPECTIVE CROSS-SECTIONAL STUDY TO DETERMINE THE BACTERIOLOGICAL PROFILE AND ANTIBIOTIC SENSITIVITY PATTERNS OF CUTANEOUS LESIONS IN IMMUNOBULLOUS DISORDERS"

BY

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UNDER THE GUIDANCE OF

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ABSTRACT

Background - The immune bullous disorders are characterized by a pathogenic immune response against structural proteins of keratinocyte.es or dermo-epidermal basement membrane zone. Septicemia and bacterial skin infections are the main causes of mortality and morbidity in immunobullous disorders.

Aim -To study the bacteriological profile of active cutaneous lesions present in immunobullous disorders and their antibiotic sensitivity patterns.

Materials and methods–A prospective cross-sectional study conducted from September 2022 to June 2024. Cases confirmed by biopsy and /or immunofluorescence with clinically active cutaneous lesions were included for culture and sensitivity

Results: Pemphigus vulgaris, pemphigus foliaceus and bullous pemphigoid were observed in 48(56.5%) ,18(21.2%) and 15 (17.6%) of the 85 patients with a diagnosis of AIBDs, respectively. The study included patients ranging in age from 0 to 85 years old. The most commonly affected groups were young adults in the 20–29 age range and older patients in the 60–69 age range, with a bimodal distribution. Females outnumbered males by a ratio of 0:0.77.

The percentage of non-sterile swabs on pus culture and sensitivity was 47.1%, which was lower than the percentage on sterile swabs (54.5%). The most common organism isolated was *Staphylococcus Aureus* (92.25%) in which 37.5% was resistant to methicillin, followed by *Pseudomonas Aeruginosa* (5%) and *Klebsiella Pneumoniae* (2.5%).Pemphigus foliaceus patients (55%) had the highest rate of bacterial growth, followed by pemphigus vulgaris (39.86%) and bullous Pemphigoid patients (33.33%).The majority of bullous Pemphigoid cases (66.67%) had sterile pus cultures, which were subsequently followed by pemphigus foliaceus (45%) and Pemphigus vulgaris (63.14%).*Staphylococcus aureus* was 100 % sensitive to antibiotics teicoplanin, linezolid, nitrofurantoin, vancomycin, tigecycline, followed by trimethoprim/sulfamethoxazole (94.44%), rifampicin (88.89%), oxacillin (88.89%), daptomycin (88.89%) and azithromycin (77.27%).The most resistant antibiotic to *Staphylococcus aureus* was benzyl penicillin (83.33%), which was followed by erythromycin (38.88%), ciprofloxacin (77.77%), and levofloxacin (61.11%).The sensitivity pattern for MRSA to vancomycin was 100% followed by tetracycline (93.33%), tigecycline (93.33%), trimethoprim/sulfamethoxazole (93.33%) and nitrofurantoin (86.67%).The

antibiotics with the highest MRSA resistance were erythromycin (73.88%), ciprofloxacin (86.777%), levofloxacin (86.67%), and benzyl penicillin (100%).

Conclusion: In 45% of the cases, bacterial growth was seen, and S. Aureus was the most commonly isolated organism. Secondary cutaneous bacterial infection was more common in Pemphigus Foliaceus. The most resistant antibiotic was benzyl penicillin, while vancomycin was 100% sensitive to MRSA.

LIST OF ABBREVIATIONS

AIBD	Autoimmune bullous disease
DEJ	Dermoepidermal junction
IF	Immunofluorescence
ELISA	Enzyme linked Immuno-sorbent Assay
SMR	Standardised mortality ratio
Dsg	desmoglein
BP	Bullous pemphigoid
PV	Pemphigus vulgaris
PF	Pemphigus foliaceus
LPP	Lichen planus pemphigoids
CBDC	Chronic bullous disease of childhood
PNP	Paraneoplastic pemphigus
DH	Dermatitis herpetiformis
BMZ	Basement membrane zone
DIF	Direct immunofluorescence
IIF	Indirect immunofluorescence
HHV	Human herpes Virus
BP 230/180	Bullous pemphigoid Antigen
LAD -1	Linear IgA Bullous Dermatosis Auto Antigen
TG3/eTG	epidermal transglutaminase
TG2/tTG	Tissue transglutaminase
IB	Immunoblotting
NHS	Normal human skin
MO	Monkey oesophagus
SIBD	subepidermal immunobullous disorder
IEM	Immunoelectron microscopy
COL 7	type VII collagen
Dsc	Desmocollin
BMF	Basement membrane fluorescence
ICF	Intercellular fluorescence
SSS	Salt-split skin

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Introduction:

Immunobullous diseases are blistering cutaneous disorders caused by pathogenic antibodies binding to protein targets within the epidermis and dermis.[1] Depending on the severity, these diseases may present with vesicles, blisters, pustules, erosions, excoriations, and erythema affecting the skin and mucous membranes.[2]

In autoimmune bullous disorders (AIBDs), autoantibodies target epidermal or dermo-epidermal junction (DEJ) components responsible for cell-to-cell adhesion. The antigen-antibody interaction triggers an inflammatory cascade that ultimately leads to vesicle formation.

AIBDs are classified as intraepidermal or subepidermal based on the level of blister formation.[3]Depending on the level of split, AIBDs can be grouped into pemphigus with autoantibodies against desmosomal adhesion molecules, pemphigoid with autoantibodies against structural proteins of the dermal-epidermal junction, and dermatitis herpetiformis, where epidermal and tissue transglutaminase are targeted.

The incidence of pemphigus in dermatological outpatients in India ranges from 0.09% to 1.8%, which show a different trend than Western literature.[4]

Accurate diagnosis is crucial for the treatment and prognosis of AIBDs. Diagnosis is based on clinical features and the presence of skin/mucous membrane-bound and circulating autoantibodies.[3]. For patients with suspected AIBD, a lesional biopsy for histopathological examination and a perilesional biopsy for IF (immunofluorescence) are indicated. Serum autoantibodies can be detected using: human salt-split skin (for pemphigoid diseases) and monkey oesophagus (for pemphigus and pemphigoid disorders). Serological analyses, such as multivariant IF microscopy, ELISA (Enzyme-linked Assay) systems, or a multistep method with separate ELISA and immunoblot assays, are necessary for a precise diagnosis.[5]

Overall mortality in pemphigus patients is 2.4 times greater than the average population, mainly due to infections.[6]The introduction of corticosteroids in the early 1950s significantly reduced mortality from 75% to 30%.7The use of immunosuppressants in the 1980s further decreased mortality to below 5% in study populations. Cause-specific standardized mortality ratios (SMRs) death in pemphigus are owing to infections (pneumonia and septicemia) as well as cardiovascular disorders.[6]

Bacteriological superficial skin infections are the most common cause of death among these patients.[8] This study aims to determine the bacterial profile in active skin lesions and their sensitivity to antibiotics, which will guide dermatologists on the appropriate usage of antibiotics and prevent resistance. Thus, this, in turn, reduces mortality and morbidity of patients with AIBDs.

AIMS & OBJECTIVES OF THE STUDY:

- To study the bacteriological profile of active cutaneous lesions, present in immunobullous disorders.
- To study antibiotic sensitivity patterns of isolated bacteria.

Review of Literature

Autoimmune bullous disorders (AIBDs) are a diverse group of diseases characterised by erosions and blisters on the skin and mucous membranes.

These diseases can be categorized into two main types: pemphigus diseases, which involve intraepidermal blistering and autoantibodies targeting desmosomal proteins such as desmoglein (Dsg) 1 and Dsg3.Subepidermal AIBDs, which include pemphigoid diseases and dermatitis herpetiformis.[5]

History:

The concept of blisters has been documented historically with terms like "pemphix" in Greek, "nufakkha" in Arabic, "ababu'oth" (bu'ah) in the Old Testament, and "pao" in ancient Chinese texts. Of these, "pemphigus," derived from the Greek root pemphix, has endured in modern medical terminology.[9]

Boissier de Sauvages (1706–1767) first introduced the term "pemphigus" in his classification of skin diseases. Hebra later divided pemphigus into pemphigus vulgaris and pemphigus foliaceus, further classifying pemphigus vulgaris into malignus and benignus. In 1881, Auspitz's classification identified pemphigus by the absence of intercellular bridges between keratinocytes, a phenomenon he termed "acantholysis." Walter Lever differentiated bullous pemphigoid (BP) from pemphigus vulgaris (PV) by noting the absence of acantholysis in BP.[9,10]

Auspitz's classification of skin diseases (1881) identified pemphigus is characterised by the absence of intercellular bridges between keratinocytes, resulting in loss of cohesiveness. He coined the term "akantholysis" to explain the phenomena. Walter Lever (1909-1992) identified a distinct difference between BP (bullous pemphigoid) and PV (pemphigus vulgaris) by observing the absence of acantholysis in the former.[9]

Pemphigus foliaceus was recognized as a distinct type by Hebra and Civatte, with Civatte identifying acantholysis in the upper epidermal layer. Neumann first described pemphigus vegetans in 1876. In 1925, Senear and Usher reported a unique form of pemphigus combining features of lupus erythematosus and seborrheic dermatitis. Lever introduced the term "pemphigoid" in 1953 to describe subepidermal bullous diseases distinct from pemphigus. Jordan and Beutner used immunofluorescence techniques to detect autoantibodies in BP patients.[9,10,11,.12]

Epidemiology:

The distribution of PV and PF varies across countries. PV affects 13% of pemphigus patients in Mali and 95% of those in Saudi Arabia [14,15]In Europe and Northern America, 65- 90% of pemphigus cases are PV, which was reviewed by Kridin (2018). In Southern America and North Africa, there is an increased incidence of PF compared to PV, hence the term endemic pemphigus.[16]In 2011, a clinic-based questionnaire survey in Kerala's Thrissur area showed an annual incidence of 4.4 per million people.[4]The epidemiology of paraneoplastic pemphigus (PNP), an uncommon pemphigus variants accounting for around 5% of cases.[17]

IgA pemphigus and pemphigus herpetiformis are far less common, with limited epidemiological data available. [18,19]

The annual incidence of BP is estimated to be between 2.4 and 23 cases per million in the general population. However, this incidence increases dramatically to 190-312 cases per million in people above the age of 80 years. Additionally, an increasing number of stuides shows an alarming trend of increased BP incidence, with a 1.9- to 4.3-fold increase over the last twenty years.[20]

Age and gender:

Pemphigus can occur at any age; however, the majority of individuals are between the ages of 45 and 65 when diagnosed.[16]Outside of endemic areas, up to 30% of patients are reported to be less than 20 years old .[21,22] Bulgaria has an average presentation age of 72.4 years, while Kuwait's average is 36.5 years.

In India, many patients are under 40 years old. In contrast to other regions of the world, pemphigus typically emerges between the ages of 40 and 60.[4]

Except for two research studies from Kuwait and Saudi Arabia, all other study cohorts showed increased proportion of females, with the F:M ratio ranging 1 and 2 and it was high as 5.0 in the United States.[23,24,25]India's gender predisposition has projected diverse outcomes. However, it appears that both sexes are equally affected.[4]

In some rural areas of South America (Brazil, Northern Colombia, and Peru) and Northern Africa, PF is not only the predominant pemphigus form, but it is also more common in the population. Four per million was the perineal incidence of pemphigus foliaceus patients in southern Tunisia.[25]

Bullous pemphigoid (BP) is the most common subepidermal autoimmune bullous disease in India and Western Europe. However , its prevalence is lower and with younger onset of age compared to West , as shown below table 1.[26]Other subepidermal autoimmune bullous disorders, such as mucous membrane pemphigoid (MMP)and linear immunoglobulin A bullous dermatosis(LABD), lichen planus pemphigoids'(LPP), pemphigoid gestationis (PG) , epidermolysis bullosa acquisita (EBA), and bullous systemic lupus erythematosus (BSLE)are pretty rare among the Indian patients .Table 1 shows data about age and gender distribution among various subepidermal blistering disorders.

TABLE 1: Age and gender distribution among various subepidermal blistering disorders[26]

Subepidermal AIBDs	Age	Male: Female
BP	59(33-80 years)	1.2;1
DH	41.5(17-75 years)	0.8:1
MMP	60(48-67 years)	1:5
CBDC	4.3(1-7 years)	3:1
LPP	63(53-70years)	1:2

Prevalence

Data on the prevalence of pemphigus are sparse. In 2006, the Danish National Patient Registry estimated that the prevalence of pemphigus was 60 per million.[16] Data on prevalence of pemphigus from India are not available.

<u>Classification of Immune-mediated bullous disorders</u>[27]:

I. **Intraepithelial blistering group of disorders**:

1. Pemphigus Vulgaris (includes pemphigus vegetans)
2. Pemphigus foliaceus:
   a. Endemic pemphigus (Fogo selvagem)
   b .Pemphigus erythematosus
3. Pemphigus herpetiformis
4. IgA Pemphigus
   a. Intraepidermal neutrophilic type
   b. Subcorneal pustular type
5. Paraneoplastic pemphigus
6. Drug-induced pemphigus

II. Subepidermal immune-mediated disorders:

1. Bullous pemphigoid
2. Mucous membrane pemphigoid
3. Linear IgA bullous dermatosis
4. Epidermolysis bullosa acquisita
5. Pemphigoid gestationis
6. Dermatitis herpetiformis

Intraepidermal blistering group of disorders:

Pemphigus and Variants

Etiology:

Pemphigus group of disorders onset and course are influenced by a complex interplay of predisposing and inducing factors.[28]

Genetic factors:

The presence of a complex polygenic basis involves multiple genetic loci, and this is well-established in AIBDs. Pemphigus vulgaris (PV) specifically shows a strong immunogenetic link with HLA class II alleles such as HLA-DRB1*04:02 and HLA-DQB1*05:03.[29]

Precipitating Factors:

Inducing or triggering environmental factors seems to be critical for disease

Precipitating factors include environmental factors such as drug intake, viral infections, physical agents, contact allergens, and food, as well as endogenous elements like emotional stress, hormonal diseases) but are somehow associated with the subject's lifestyle. Various drugs can cause acantholysis due to alteration in keratinocyte membrane biochemistry (biochemical acantholysis) and or with the immune balance (immunologic acantholysis). The host's release of interferons and cytokines in response to the viral infection, which will activate the immunological response acts as a precipitating factor.[28]

PV can be precipitated by various physical agents including, ultraviolet or ionising radiation, thermal or electrical burns, surgery and cosmetic procedures. Contact allergens such as organophosphate pesticides, dietary factors (e.g., garlic, leek, onion, black pepper, red chilli pepper, red wine, tea), and emotional stress have been implicated. Although these events are rare but well recorded in literature. [28]

Subepidermal immune-mediated disorders

Bullous Pemphigoid and variants

A complex interaction between predisposing and inducing factors determines the onset and course of bullous pemphigoid. The most important genetic factor for predisposition to autoimmunity is HLA genes. Various studies have found association between HLA-DQβ1*0301 and specific clinical pemphigoid variants.[30]

Drugs can trigger immunological responses or affect the antigenic properties of the epidermal basement membrane. For example, gliptins, PD-1/PD-L1 (programmed cell death proteins) inhibitors, loop diuretics, penicillin and derivatives.[31]

Physical agents such as radiation therapy, ultraviolet radiation, thermal or electrical burns, surgical procedures, and transplants can cause BP, which is a rare but well-documented event.

Infections such as human herpes virus (HHV) (cytomegalovirus, Epstein-Barr virus, and HHV-6), hepatitis B and C viruses, Helicobacter pylori, and Toxoplasma gondii may contribute to BP induction. Unlike pemphigus, no dietary cues have been linked to the induction of BP.[30]

Dermatitis Herpetiformis

The HLA DQ2 or HLA DQ8 alleles are inherited and represent the most likely genetic link in this association, a connection that has also been observed in animals[32].Gluten exposure is the primary environmental factor that causes the disease. Certain DH triggers, like UVB exposure and trauma, can increase IL-8 production, leading to the formation of cutaneous lesions.[33]

Pathogenesis:

Epithelial Biology:

An understanding of pemphigus requires a basic understanding of oral and cutaneous epithelial biology. Three complex structures—nexus junctions (gap junctions), adherens (desmosomes and adhesion plaques), and occludens (tight junctions)—help the keratinoctyes to connect with one another.[34]

Desosomes:

Desmosomes are essential for epithelial integrity by serving as an adhesive complex and a cell-surface attachment site for the cytoskeleton's keratin intermediate filaments.

Desmosomes are composed of adhesion proteins, mainly desmogleins and desmocollins, glycoproteins of the cadherin supergene family that attach to cytokeratins via desmoplakins and plakoglobin.[35], shown below in Figure.1.

Cadherins, on the other hand, consist of an extracellular domain involved in calcium-dependent interaction with the neighbouring cells, a transmembrane domain, and an intracellular domain that binds to catenins and actin.[36] In the skin, both desmoglein 1 (Dsg 1) and desmoglein 3 (Dsg 3) are expressed, whereas the oral epithelium primarily expresses Dsg

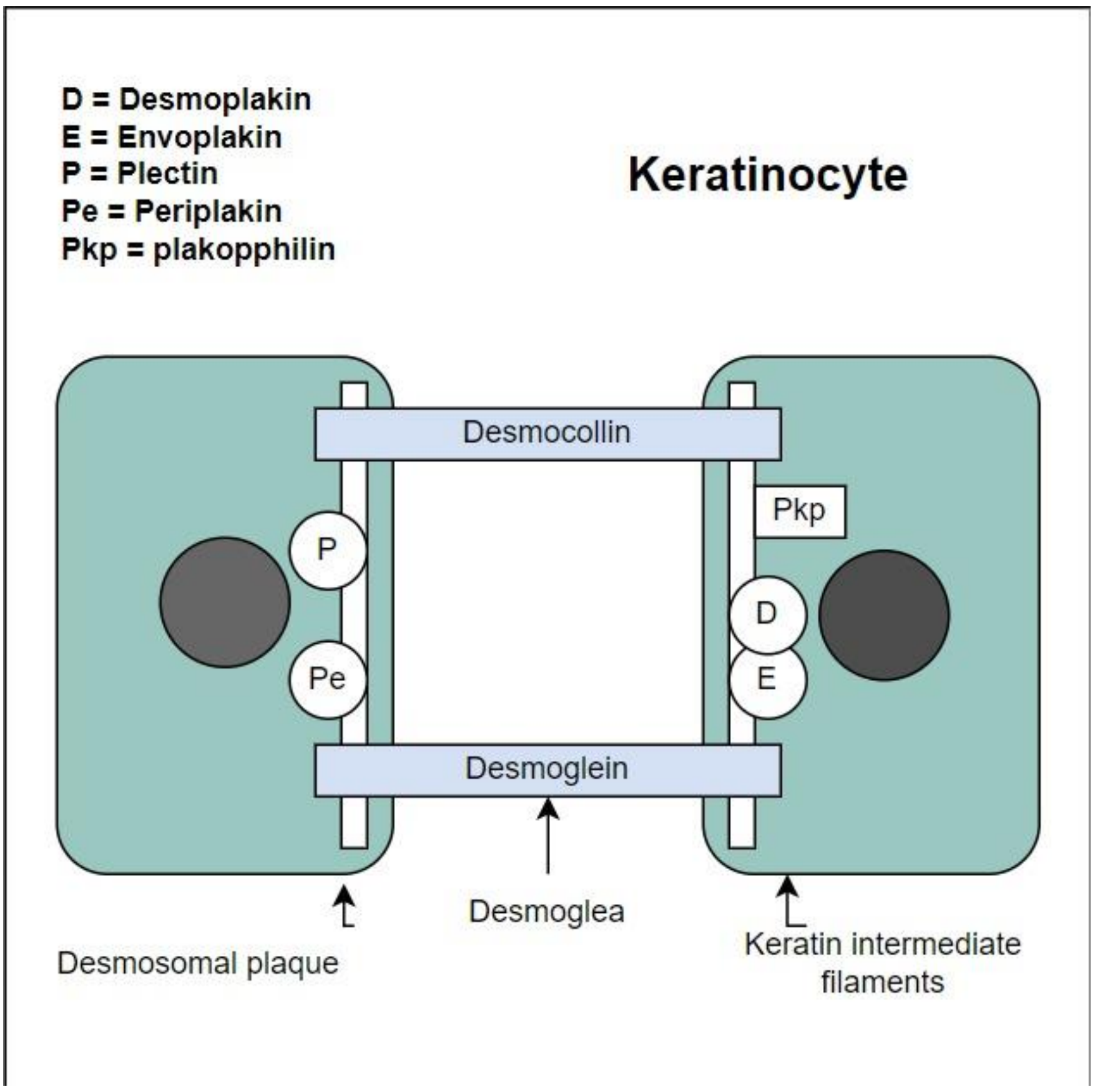


Fig.1 structural proteins in between two keratinocytes

Pemphigus is an autoimmune bullous disorder characterized by antibodies targeting the extracellular domains of cadherin-type epithelial cell adhesion molecules known as desmogleins (Dsg). This immune reaction leads to desmosomal damage, intra-epithelial immune deposits, and loss of cell-cell contact (acantholysis), resulting in intra-epithelial blister formation.[37]

Pemphigus vulgaris (PV) leads to intercellular deposition primarily of IgG class antibodies. These antibodies target the extracellular domains of cadherin-type epithelial cell adhesion molecules, specifically desmoglein 3, resulting in damage to desmosomes. Primarily, Dsg 3 antigen is present in oral mucosa; however, the skin has both Dsg 1 and Dsg 3 antigens. Autoantibodies against Dsg 3, as in PV, result in oral lesions at an early stage, whereas skin is intact due to compensation by Dsg 1 antigen. But antibodies appear against Dsg 3, cutaneous lesions develop, and the disease is more severe.[34]Pemphigus pathogenesis involves T-helper 2 cells producing activated B-cells and IgG in response to IL-4 activation. Patients with pemphigus foliaceus only produce autoantibodies against Dsg1.Hence has very rare oral involvement.[38]

PNP is differs from PV and PF in that it may have autoantibodies to Desmogleins 1 and 3, but it also has more specific antibodies to envoplakin and periplakin. PNP also has autoantibodies against desmosomal proteins, including members of the plakin family (plectin, BP230, and desmoplakin), desmocollins, and alpha-2-macroglobubin-like antigen-1.[38]Table 2 summarizes all the target antigens in intraepidermal blistering disorders.

TABLE 2: Intraepidermal blistering disorders and target antigens[2,3,5]

Disease	Target autoantigen
Pemphigus Vulgaris	Dsg 3 >Dsg 1
Pemphigus Foliaceus	Dsg 1
IgA Pemphigus	Dsc 1, 2, 3; Dsg 1, 3
PNP	Dsg 3, periplakin, desmoplakin I/II, α-2-macroglobulin-like antigen-1, envoplakin, plectin, Dsc1, 2, 3

Dsg – desmoglein ,Dsc - Desmo Collin

Bullous Pemphigoid

The Th17/IL-17 pathway, the stimulation of toll-like receptors, and a disparity between autoreactive T helper and T regulatory cells are the main immunological triggers for BP. The pathogenesis of BP involves an autoantibody production to hemidesmosome structural components (BP180 and BP230). Autoantibodies bind and activate complement, recruit inflammatory cells, and release proteolytic enzymes. Th17 cell activation may induce the inflammatory cascade without the involvement of autoantibodies. The inflammatory cascade induces complement activation and mast cell degranulation. Following that, eosinophils and neutrophils are recruited, which release proteolytic enzymes such as neutrophilic elastase and matrix metaloproteinase-9, resulting in subepidermal blistering.[30]

TABLE 3: Subepidermal blistering disorders and target antigens[2,3,5]

Disease	Target Antigen
Bullous pemphigoid	BP180, BP230
Mucous membrane pemphigoid	BP180, (LAD-1), laminin 332, BP230, α4β6-Integrin
Pemphigoid gestationis	BP180 NC16A, BP230
Anti-p200/ laminin γ1 pemphigoid	p200 protein, laminin γ1
Linear IgA disease	BP180 (LAD-1), type VII collagen
Epidermolysis bullosa acquisita	Type VII collagen

BP 180/230- Bullous pemphigoid Antigen LAD-1 - Linear IgA Bullous Dermatosis Auto Antigen

Dermatitis Herpetiformis

Tissue transglutaminase (TG2/ tTG), present in the gut, is the main autoantigen in Coeliac disease. After absorption into the lamina propria of the gastrointestinal tract (GIT), TG2 converts glutamine to glutamic acid inside gliadin, an alcohol-soluble gluten portion. Gliadin is then presented to CD4+ T-cells, leading to inflammation and the apoptosis of mucosal epithelial cells. The modified glutamine residues of gliadin cross-link with TG2 and are presented with gliadin-specific helper T-cells, which subsequently triggers the B-cells to form circulating IgA antibodies directed against TG2 and circulating IgA autoantibodies targeting the epidermal transglutaminase (TG3/eTG), is present in the skin. Unlike TG2 in CD, TG3 is the main autoantigen in DH.[33]Table 3 depicts all target antigens present in subepidermal blistering disorders.

<u>Clinical Features:</u> In detail descriptions of clinical feature of all AIBDs is given below table 4.

<u>Table 4:</u> Description of clinical features of various AIBDs[4,27]

Pemphigus and Variants	Clinical presentations
Pemphigus vulgaris	Erosions of mucous membranes, flaccid blisters/erosions of the skin
Pemphigus foliaceus	Flaccid blisters/erosions of the skin, scaling erosions and plaques in seborrheic areas of distribution
IgA pemphigus	Pustules predominant distribution in intertriginous areas. Fragile, annular, vesicles or pustules, or crusted erosions on the skin; rarely involves mucous membranes
Paraneoplastic pemphigus (PNP)	Recalcitrant oral stomatitis, polymorphic cutaneous lesions including → lichenoid lesions predominant acral distribution ; common associations: haematologic malignancy and solid malignancy like thymoma, Castleman tumour
Pemphigoid and Variants	
Bullous pemphigoid	Tense blisters, erosions, erythema, urticarial plaques, severe itch
Mucous membrane pemphigoid	Predominant mucous membrane lesions (oral > conjunctival > nasal) Erosions and ulcers with mucous membrane atrophy (conjunctivitis, symblephara), skin involvement in 25% of cases, head, and upper trunk.

Pemphigoid gestationis	Vesicles, urticarial plaques, erythema mainly in the periumbilical area; severe itch
Anti-p200/ laminin γ1 pemphigoid	As in bullous pemphigoid
Linear IgA disease	Vesicles at the lesion margins (string of pearls sign) sometimes; otherwise like bullous pemphigoid
Epidermolysis bullosa acquisita	Tense vesicles and red raw areas on skin and mucous membranes Two types: Mechanobullous, inflammatory type or atrophic type, common involvement of mucous membranes; scarring and milia formation
Dermatitis herpetiformis (DH)	Prominent papule or vesicles on extensor aspect of body or small blisters; erythematous plaques, intense pruritus; coeliac disease may not be evident clinically

;

Diagnosis:

Histopathology

Histopathology of a lesional skin biopsy can distinguish between pemphigus and subepidermal blistering.[4]An early vesicle's histopathological examination demonstrates the level of split as well as the presence and composition of an inflammatory infiltrate. However, histopathological examination (HPE) frequently does not yield an accurate diagnosis in every case. Investigations to detect tissue bound or circulating antibodies should be performed for final confirmation of the diagnosis[39,40]

Immunofluorescence tests

IF has become an essential tool in diagnosing the AIBDs. It is commonly used to complement the clinical and histological diagnosis of various vesiculobullous disorders. Additionally, along with confirmation of the diagnosis, it also provides a basis for other advanced tests, such as ELISA and IB (immunoblotting), provided necessary facilities are available.[40]

Direct immunofluorescence

The gold standard test identifies the antibodies bound in vivo to the tissue antigens in the biopsy specimen, thereby confirming the diagnosis of AIBDs.[40]Five features are used to comprehend the results: the class of immunoglobulin, the number of immune deposits, the patterns of the immune deposit (granular or linear), the locations of immune deposition, and deposition in sites other than the primary site. Utilizing these factors, a pattern approach will help in diagnosis in the majority of specimens.[40]

Indirect immunofluorescence

IIF is a two-step serological approach that detects circulating antibodies. The patient's serum is diluted with phosphate-buffered saline in serial dilutions (beginning at 1:10) and then incubated with an appropriate substrate. IIF's sensitivity is often lower than DIF's and differs based on the substrate applied. However, in pemphigus, sensitivity can be improved by combining substrates, like normal human skin (NHS) and monkey oesophagus (MO).[42]

Salt-split technique

This technique involves incubation of skin in 1M sodium chloride for 48–72 h, leading to a split in the skin between the epidermis and dermis at the level of lamina Lucida. This simple procedure is highly helpful for categorizing subepidermal immunobullous disorders (SIBDs) .Some antigens attach to the epidermal side ('roof') of the split, while others migrate to the dermal side ('floor'). SIBDs can be identified as "roof-" or "floor-" binding patterns based on the position of the BMZ band in relation to the split. [40,43]

Enzyme-linked immunosorbent assay

Recently, recombinant and cell-derived forms of the target antigens have been employed to develop sensitive and specific ELISA for identifying circulating autoantibodies.[40]

ELISA is a quantitative assessment for the determining the specific circulating antibody levels, similar to IIF. Hence, ELISA is helpful for both diagnosing and monitoring disease activity. The drawback of ELISA is that it may not identify all cell surface antibodies involved in the pathogenesis of AIBD; unlike IIF, it may detect antibodies directed against a wide range of nonpathogenic antigens present in normal epithelium. As a result, ELISA should be used as a supplementary test to IIF rather than a substitution.[40]

Others

The molecular weight of the target antigen in AIBDs can be determined using immunoblotting and immunoprecipitation methods. Immunoelectron microscopy (IEM) demonstrates the precise ultrastructural location of antigens in AIBDs.A brief summary of all investigations HPE, DIF , IIF and ELISA of various AIBDs is shown in table 5.

Table 5: Histopathogical features and Immunofluorescence findings in AIBDs[4,27,43,44,45]

Disease	**Histopathological features**	**Immunofluorescence tests**
Pemphigus vulgaris	Suprabasilar acantholysis. Since basal keratinocytes adhere to the hemidesmosome, they create a pattern known as "tombstoning."	• DIF: ICF IgG/C3 • IIF monkey esophagus: ICF IgG • ELISA, IIF: Dsg3+ Dsg1±
Pemphigus foliaceus	Subcorneal acantholysis, with the split taking place within the granular layer	• DIF: ICF IgG/C3 • IIF monkey esophagus: ICF IgG • ELISA, IIF: Dsg1+
IgA pemphigus	Mild acantholysis and neutrophilic infiltration in the epidermis IEN type: suprabasilar pustules in the lower or complete epidermis are present. SPD type: pustules are sub corneally positioned in the upper epidermis.	• DIF: ICF IgA/C3 • IIF monkey esophagus: ICF IgA • ELISA, IIF: Dsc1, 2, 3 Dsg 1, 3 IgA+
Paraneoplastic pemphigus	a pattern of vacuolar or lichenoid interface dermatitis.	• DIF: ICF IgG/C3 ± BMF

	Acantholysis and intraepidermal cleft , and subepidermal blisters, which are less common.	• IIF monkey esophagus: ICF IgG ± BMF Rat/monkey bladder: urothelium + • ELISA, IIF: Dsg3+, envoplakin +
Pemphigoid diseases		
Bullous pemphigoid	Subepidermal bullae with eosinophils +/- neutrophils in upper dermis	• DIF: BMF • IIF monkey oesophagus: BM florescence • IIF SSS: roof of blister • ELISA, IIF: BP180+, BP230+
Mucous membrane pemphigoid	Same as BP	• DIF: BMF, n-pattern • IIF monkey esophagus: BMF • IIF SSS: roof of blister and/or floor of blister ELISA: BP230+ BP180+. IB: LAD-1 IB, IIF: laminin332+
Pemphigoid gestationis	Same as BP	• DIF: n-pattern, BM florescence

		• IIF monkey oesophagus: Basement florescence • IIF complement-SSS: roof of blister • ELISA, IIF BP180+, BP230+
Anti-p200/ laminin γ1 pemphigoid	Same as BP	• DIF: n-pattern, BM • IIF monkey oesophagus: BM • IIF SSS: blister floor • IB: p200+
Linear IgA disease	Subepidermal bullae with neutrophils evenly distributed in upper dermis	• DIF: BMF, n-pattern • IIF monkey oesophagus: BM • IIF SSS: roof of blister • IB, ELISA: BP180+(IgA), LAD -1
Epidermolysis bullosa acquisita	Subepidermal bulla with neutrophils	• DIF: u-pattern • IIF monkey esophagus: BMF • IIF SSS: blister floor ELISA, IIF: COL7+
Dematitis herpetiformis	Subepidermal bullae with papillary tip	Granular IgA deposits at pappilary tips

	neutrophilic microabscess	

BMF: basement membrane fluorescence, COL-17, type VII collagen, Dsc: desmocollin, Dsg: desmoglein, DIF/IIF: direct/indirect immunofluorescence microscopy, GAF: coeliac disease-specific gliadin epitopes, IB: immunoblotting, ICF: intercellular fluorescence, LAD-1: soluble ectodomain of BP 180, SSS: salt-split skin

.

Secondary bacterial infection in AIBDs

- Septicemia and bacterial skin infections are the main causes of mortality and morbidity in these patients.[47]The changing bacteriological profile and antibiotic sensitivity patterns necessitate systematic research at regular intervals.
- The challenges to global public health in the twenty-first century have brought to light the rising threat of antimicrobial resistance, which makes patients more prone to bacterial infections that could previously be treated with available antibiotics.[48]
- The incidence of resistant bacterial pathogens is rising, which necessitates that pattern of infection and bacteriological profiles of cutaneous lesions be reviewed periodically, and the information used to guide dermatologists regarding antibiotic usage.[49]

Treatment:

Chronic autoimmune bullous diseases can have a substantial morbidity and mortality rate in patients who fail to receive treatment. Introduction of immunosuppressive drugs, as decreased mortality rate significantly. However, adverse reactions from the drugs are common causes of morbidity in these patients. Consequently, individuals with autoimmune bullous disorders have limited treatment options due to the need for long-term drugs regimens that have adverse effects. [509]Summary of treatment guidelines is depicted in table 6.

Systemic Steroids

For all of AIBDs, glucocorticoids are the cornerstone of therapy. As they inhibit the production of proinflammatory cytokines, they have anti-inflammatory and immunosuppressive effects. They decrease T-cell lymphocyte reactivity to antigens and decrease the number of circulating T-cell lymphocytes. Glucocorticoids also reduce the synthesis of antibodies.

Patients who are immunosuppressed are more susceptible to infections. Prolonged use may also cause acid reflux, cushingoid fat redistribution, osteoporosis, and osteonecrosis of neck of femoral bone. In addition, hyperglycaemia, hypertriglyceridemia, proximal myopathy, hyperactivity, glaucoma, and cataracts may develop in patients.[51]

Azathioprine

Azathioprine is urine analog that serves as a steroid-sparing agent for vesiculobullous diseases. It is a prodrug, which means it is converted in the body to its active forms. First it is converted to 6-mercaptopurine, later metabolized to 6-thioguanine. The active metabolite, thioguanine inhibits the synthesis of adenine and guanine nucleotides, azathioprine acts during the S-phase of the cell cycle. The dosage range is 2-3mg/kg/body weight. It takes a while to start working; normally six to eight weeks are needed. Every two weeks, initial monitoring should include a complete blood count (CBC) and liver enzyme tests. Alopecia, hepatotoxicity, pancreatitis, gastrointestinal toxicity and bone marrow suppression are among the uncommon side effects of azathioprine.[52]

Mycophenolate mofetil (MMF)

Through noncompetitive inhibition of inosine monophosphate dehydrogenase (IMPDH), MMF suppresses de-novo purine production. MMF primarily affects B-cell and T-cell lymphocytes since they do not have a purine salvage pathway. Compared to other immunosuppressive drugs, this one might be considered safer because the salvage pathway is still active. At 0.5 - 1.5g should be taken twice a day. Following consumption, MMF is changed into mycophenolic acid, which the liver then metabolises.

The most common adverse effect of MMF, which is well tolerated, is gastrointestinal distress. Leukopenia, thrombocytopenia, and dose-related, reversible anaemia are side effects.[53]

Cyclophosphamide

During the cell cycle, it is an alkylating agent that attaches to DNA in a non-specific way. This nitrogen mustard derivative stops the cell cycle and triggers apoptosis in cells that multiply quickly, such as lymphocytes.

Acute myelosuppression is common. Mucosal ulcers, alopecia, nephrotoxicity, cardiotoxicity, hepatotoxicity, and interstitial lung fibrosis are other adverse effects. Male patients may very rarely get azoospermia.

Up to 40% of patients experience hemorrhagic cystitis, which is associated with the development of transitional cell carcinoma.[54]

Cyclosporine

It is an immunosuppressive drug that inhibits T-cell lymphocytes. By forming a compound with cytoplasmic cyclophilin, it prevents calcineurin from being activated. NFAT-1, a transcription factor that starts the synthesis of IL-2 and stimulates the proliferation of helper and cytotoxic T-cells, is typically phosphorylated by activated calcineurin.

Electrolyte imbalances, including hyperkalaemia, hyperuricemia, and hypomagnesemia, are the most frequent adverse reactions. Nephrotoxicity is a dose-related side effect of cyclosporine that may initially be reversible. Tremors, hirsutism, hyperlipidaemia, hypertension, and gingival hyperplasia are other side effects.[55]

Dapsone

A sulfone antibiotic, dapsone primarily acts against polymorphonuclear leukocytes to reduce inflammation. Through inhibition of myeloperoxidase activity, the medication prevents neutrophil toxicity and chemotaxis.

All patients experience variable degrees of methemoglobinemia and haemolytic anaemia as a common side effect. Patients with glucose-6-phosphate dehydrogenase deficiency have the most severe symptoms, which are dose-related. Dapsone is also linked to psychosis and idiosyncratic peripheral motor neuropathy. During the first three months of treatment, agranulocytosis is an uncommon but serious side effect.Last but not least, a dapsone hypersensitivity syndrome may manifest, encompassing severe symptoms akin to mononucleosis, including fever, erythroderma, hepatitis, eosinophilia, or even death.

Rituximab

It is a chimeric, murine/human monoclonal antibody produced through genetic engineering.Rituximab targets CD20-positive B cells specifically, which causes their depletion and subsequent immune response regulation. Rituximab is an effective treatment for establishing disease remission and reducing the need for long-term immunosuppressive medication because it interferes with the B cell-mediated immune response.[57]

Intravenous immunoglobulin (IVIG).

High-dose IVIG is made from pooled plasma and is a human source of pure immunoglobulin G (IgG). Three separate procedures are used to inactivate and eliminate viral contaminants, such as the human immunodeficiency virus and hepatitis, from IVIG preparation. It is administered as a gradual IV infusion over the course of three to five days, at a dose of 2g/kg every cycle. Every four weeks, the treatment is repeated.

Multiple theories exist;however, the exact mechanism is unknown.

Renal failure and transfusion-related acute lung injury (TRALI), which is rare, are potential side effects of IVIG. Premedication with steroids or antihistamines is recommended if there has previously been a history of infusion reactions.

Fever, headache, myalgia, nausea, tachycardia, hemolysis, aseptic meningitis, thrombotic event, and anaphylaxis are some other uncommon side effects.[57]

Treatment guidelines for all AIBDs is show below in table 6.

TABLE 6: Treatment guidelines for various AIBDs

Disease	Line of therapy	Drugs
Pemphigus Vulgaris	First Line	High dose Corticosteroids Azathioprine MMF
	Second Line	Rituximab IVIg Cyclophosphamide Chlorambucil Plasmapheresis
	Third Line	Dapsone Cyclosporine
Pemphigus Foliaceus	First Line	Systemic Corticosteroids
	Second Line	Azathioprine MMF
Paraneoplastic Pemphigus	First Line	High dose Corticosteroids Azathioprine
	Second Line	MMF IVIg High dose Chlorambucil
	Third Line	Plasmapheresis Rituximab

Bullous Pemphigoid	First Line	Systemic Corticosteroids Dapsone Azathioprine MMF
	Second Line	Methotrexate IVIG
Dermatitis herpetiformis	First Line	Dapsone Gluten Free Diet Sulphapyridine Tetracycline /Nicotinamide
	Second Line	Cyclosporine Colchicine Systemic Steroids
Linear IgA dermatosis	First Line	Dapsone Sulphapyridine Colchicine
	Second Line	Tetracycline /Nicotinamide
Epidermolysis bullosa acquisita	First Line	Systemic Corticosteroids Azathioprine Supportive therapy / Avoidance of trauma
	Second Line	Methotrexate

		Cyclophosphamide Colchicine Cyclosporine
	Third Line	Immunoadsorption /Rituximab

IVIG – Intravenous Immunoglobulin

METHODOLOGY

SOURCE OF DATA:

Inpatients and outpatients in the Department of Dermatology, Venereology, and Leprosy, Shri B.M. Patil Medical College, Hospital and Research Center

Period of study:

The study was conducted from September 2022 to June2024.

Study design: Prospective cross-sectional study

Sample size:

With anticipated sensitivity to tetracycline 66.6%,[3] the study required a sample size of **85 subjects** with 95**%** level of confidence and 10% absolute precision, Using Statulator software **(**http://statulator.com/SampleSize/ss1P.html)

Formula used

$$n = \frac{z^2\, p*q}{d^2}$$

Where Z= Z statistic at α level of significance

d^2= Absolute error

P= Proportion rate

q= 100-p

Statistical Analysis

- The data obtained was entered into a Microsoft Excel sheet, and statistical analysis was performed using the software JMP®, Version 16. SAS Institute Inc., Cary, NC, 1989-2021.

Results are presented as Mean ±SD, Median and interquartile range, frequency, percentages, and diagrams

METHOD OF COLLECTION OF DATA:

Inclusion criteria:

Cases confirmed by biopsy and /or immunofluorescence with clinically active cutaneous lesions areincluded.

Cases were including **intraepidermal** blistering disorders like pemphigus and its variants and **sub-epidermal** blistering disorders like bullous pemphigoid, cicatricial pemphigoid, linear IgA disease, dermatitis herpetiformis, pemphigoid gestationis, lichen planus pemphigoides, epidermolysis bullosa acquisita , and bullous systemic lupus erythematosus [1].

Exclusion criteria

Patients having only crusted or dried cutaneous lesions.

Patients having only active mucosal lesions.

Methods

Informed consent for the study was obtained from the patients. All subjects underwent a complete clinical and cutaneous examination. These findings were recorded in the proforma. Clinical samples were collected using a sterile cotton swab stick following universal aseptic precautions and sent to the microbiology lab, Shri B M Patil Medical College, Hospital, and Research Center.

METHODOLOGY

Eighty-five samples were gathered from the active skin lesions of both inpatients and outpatients suffering from immunobullous disorders at the Department of Dermatology, Venereology, and Leprosy at Shri B M Patil Medical College, Hospital, and Research Centre in Vijayapura, Karnataka. All collected samples were transported in capped plastic tubes and then processed in the microbiology lab. Gram staining was done to identify gram-positive or negative bacteria. Culture specimens were inoculated onto blood agar, Mac-Conkey agar, and nutrient agar media by standard technique.[10] All cultures were observed for growth after 24 hours of incubation. Further identification and antimicrobial susceptibility pattern of bacteria was made using the fully automated VITEK 2 machine (bioMerieux).[10]

ETHICAL CLEARANCE BEEN OBTAINED FROM BLDE UNIVERSITY:

YES (BLDE(DU)/IEC/698/2022-23)

RESULTS

A hospital based prospective cross-sectional study was conducted from September 2022 to June 2024.

A total of 85 patients with AIBDs were included in the study

Distribution of cases

Of the eighty-five patients diagnosed with AIBDs, the distribution of cases included in the study: PV 48 (56.5%), PF 18 (21.2%), BP 15 (17.6%), EBA 1 (1.2%), LABD 2 (2.4%), and neonatal pemphigus 1 (1.2%), respectively in shown figure 3 and table 7.

Table 7: Distribution of cases

DIAGNOSIS	FREQUENCY	PERCENT
NPV	1	1.2
EBA	1	1.2
LABD	2	2.4
BP	15	17.6
PF	18	21.2
PV	48	56.5
Total	85	100.0

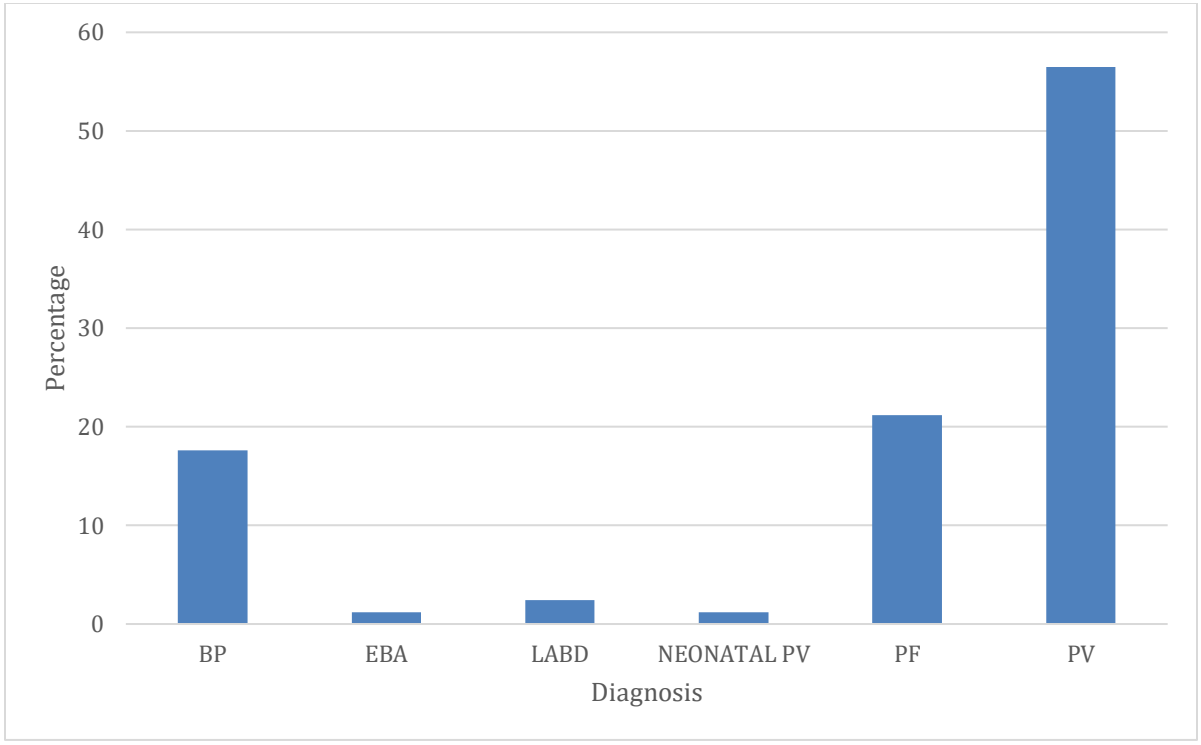


Figure 3: Distribution of cases

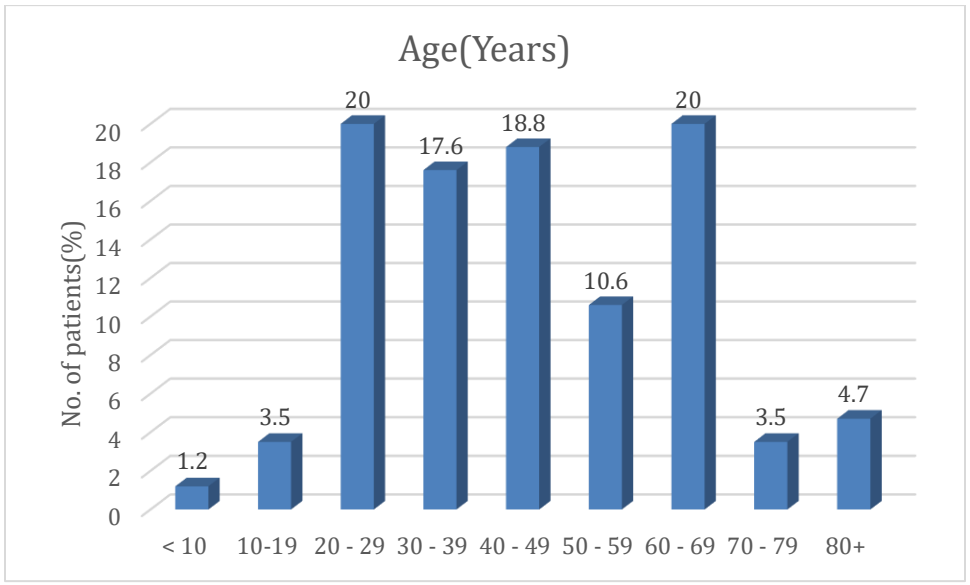
AGE DISTRIBUTION:

The age of the patients enrolled in the study ranged from 10 days to 85 years with a mean age of 45.28 years. Age distribution of the patients included in the study is presented in Table 8 and Figure 4. Population in the age group between 20 to 29 and 60 to 69 years constituted the majority of the study subjects.

Table 8: Age (years) distribution

Age(Years)	No. of patients	Percentage
< 10	1	1.2
10 – 19	3	3.5
20 – 29	17	20.0
30 – 39	15	17.6
40 – 49	16	18.8
50 - 59	9	10.6
60 - 69	17	20.0
70 - 79	3	3.5
80+	4	4.7
Total	85	100.0

Figure 4: Age distribution in AIBDs



Gender distribution:

Among 85 patients, 37 (43.5%) were males and 48 (56.5%) were females. The gender distribution of the participants in the study is presented in Table 9 and Figure 5.

Table 9: Gender distribution in study population

	No. of patients	Percentage
F	48	56.5
M	37	43.5
Total	85	100.0

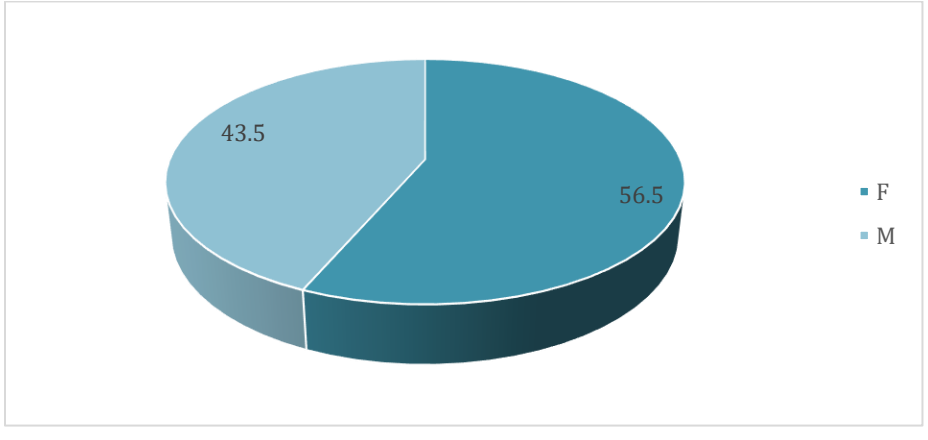


Figure 5: Distribution of patients based on gender

Pus culture:

Out of 85 swab samples sent for pus culture and sensitivity, 45 (52.9%) were sterile and 40 (45.2%) were non-sterile, as shown in Table 9 and Figure 6.

Table 9: Pus culture

Pus culture after 48 hours of incubation	PERCENTAGE
STERILE	52.9
NON-STERILE	47.1

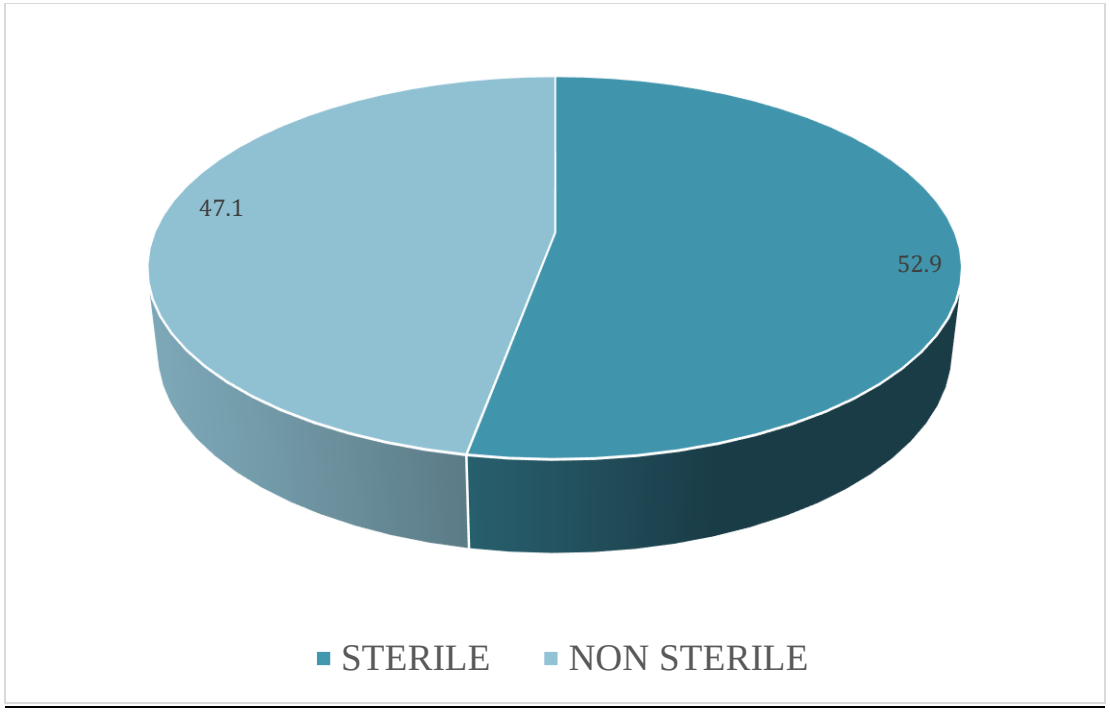


Figure 5: Pus Culture

Microorganisms cultured:

Of the 40 samples that exhibited bacterial growth, 37 had *Staphylococcus aureus*, of which 15 (37.5%) were methicillin-resistant, 3 (7.5%) were coagulase-negative, and 1 (2.5%) contained *Staphylococcus epidermidis*. These results are displayed in Table 10 and Figure 6.

Table 10: Microorganisms cultured

Pus culture	Frequency	Percent
Klebsiella pneumoniae	1	2.5
Pseudomonas aeruginosa	2	5
Coagulase negative *Staphylococcus*	3	7.5
Methicillin resistant *Staphylococcus aureus*	15	37.5
Staphylococcus aureus	18	45
Staphylococcus epidermidis	1	2.5
Total	40	100.0

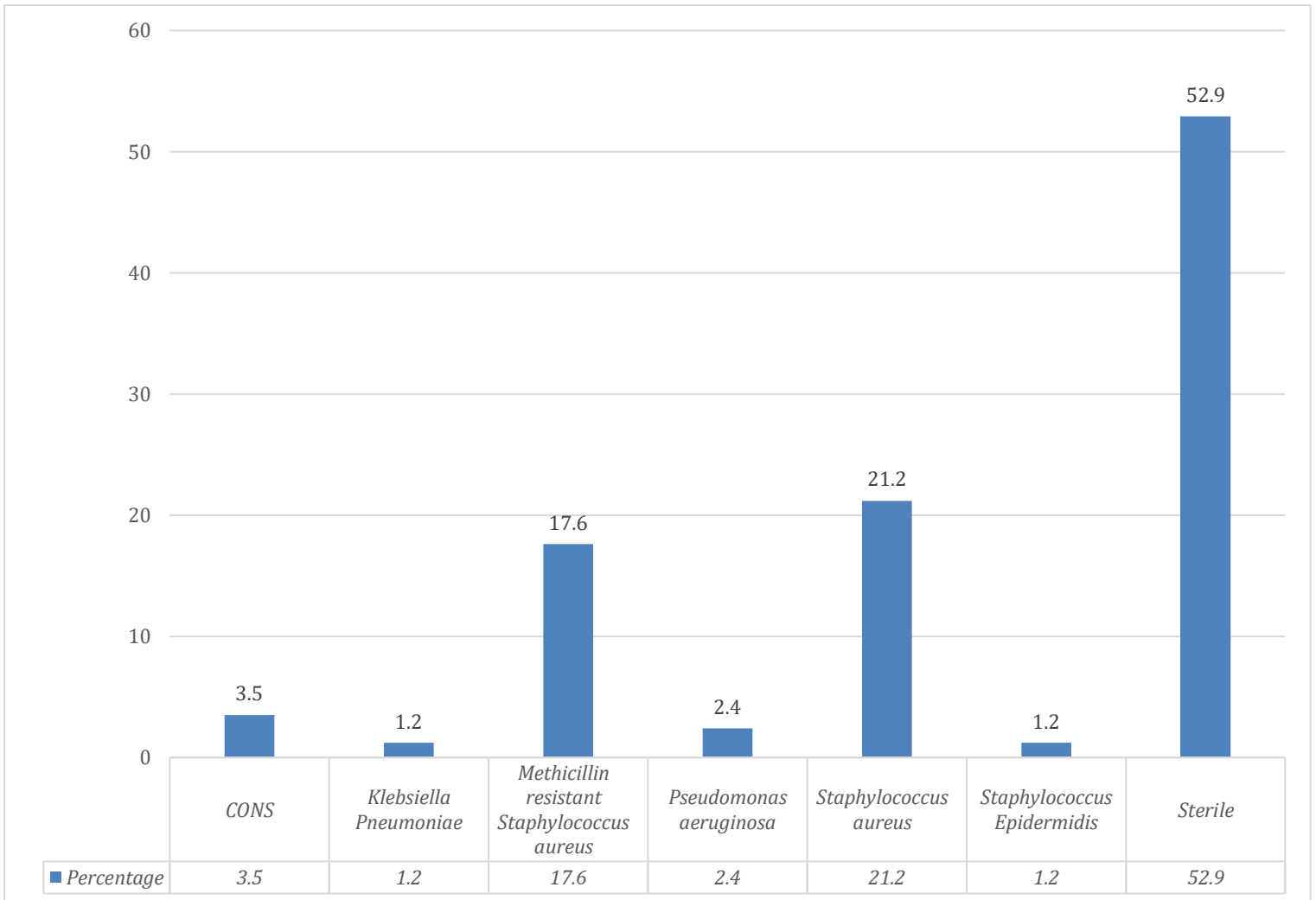


Figure 6: Microorganisms cultured

Microorganism isolated from lesions Pemphigus vulgaris:

Pemphigus vulgaris cases on pus culture showed no growth in 29 (60.14%) and growth in 19 (39.86%) cases, as Table 11 and Figure 7 illustrate.

Table 11: **Microorganisms isolated from lesions in pemphigus vulgaris**

Pemphigus Vulgaris	Number of cases	Percentage
Sterile	29	60.14
Staphylococcus aureus	8	16.66
Methicillin resistant *Staphylococcus aureus*	5	10.41
Pseudomonas aeruginosa	2	4.16
Coagulase negative *Staphylococcus aureus*	2	4.16
Klebsiella pneumoniae	1	1.25
Staphylococcus epidermidis	1	1.25
Total	48	100

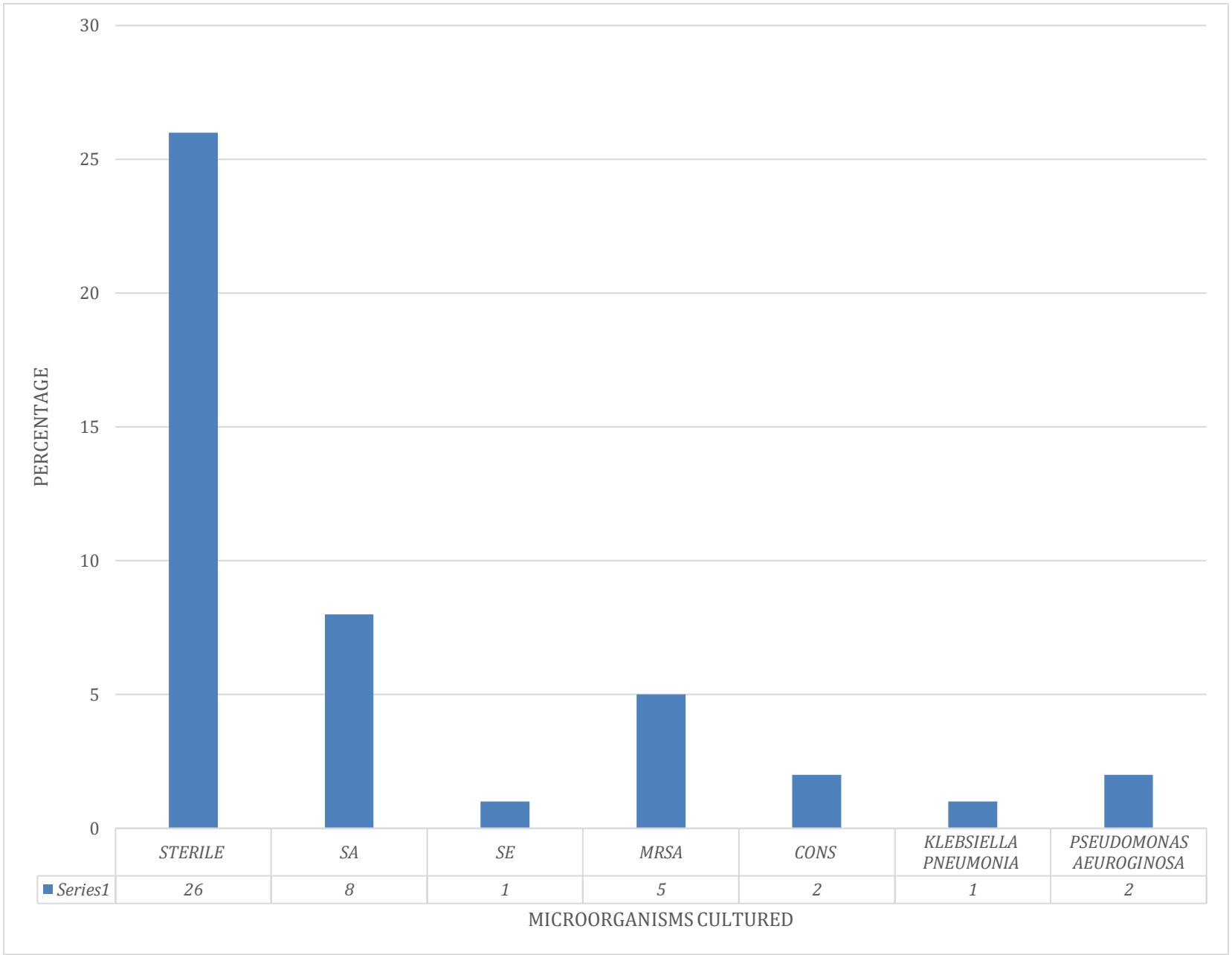


Figure 7: Microorganism isolated from lesions in pemphigus vulgaris

Microorganism isolated from lesions in Pemphigus Foliaceus:

Pemphigus foliaceus cases on pus culture and sensitivity, 8 (44.44%) cases showed no growth and 10(55.56%) cases showed growth, as depicted in table 12 and figure 8.

Table 12: **Microorganisms isolated from lesions in Pemphigus Foliaceus:**

Pemphigus Foliaceus	Number of cases	Percentage
Sterile	8	44.44
Staphylococcus aureus	7	38.33
Methicillin resistant *Staphylococcus aureus*	3	16.67
Total	18	100

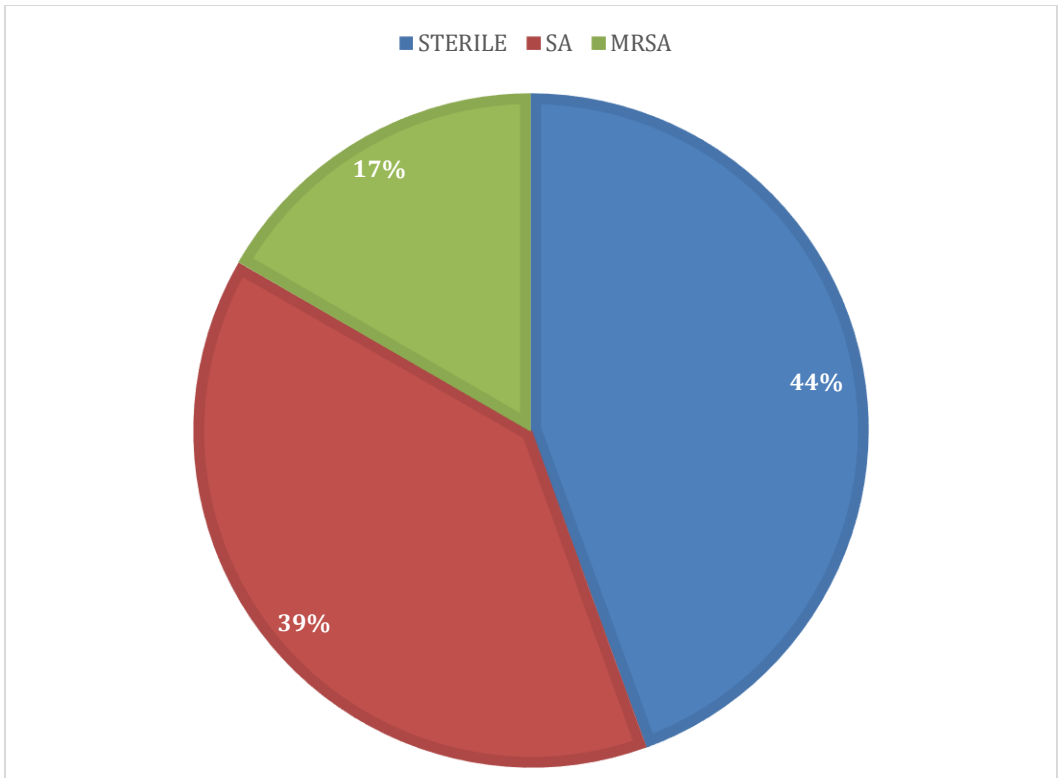


Figure 8: Microorganisms isolated from lesions in Pemphigus Foliaceus:

Microorganisms isolated from lesions in Bullous Pemphigoid:

The data on bullous pemphigoid cases is displayed in Table 13 and Figure 9. Ten patients (66.67%) on pus culture showed no growth, while five cases (33.33%) exhibited growth

Table 13: **Microorganisms isolated from lesions in Bullous Pemphigoid:**

Bullous Pemphigoid	Number of cases	Percentage
Sterile	10	66.67
Staphylococcus aureus	3	20
Methicillin resistant *staphylococcus aureus*	2	13.33

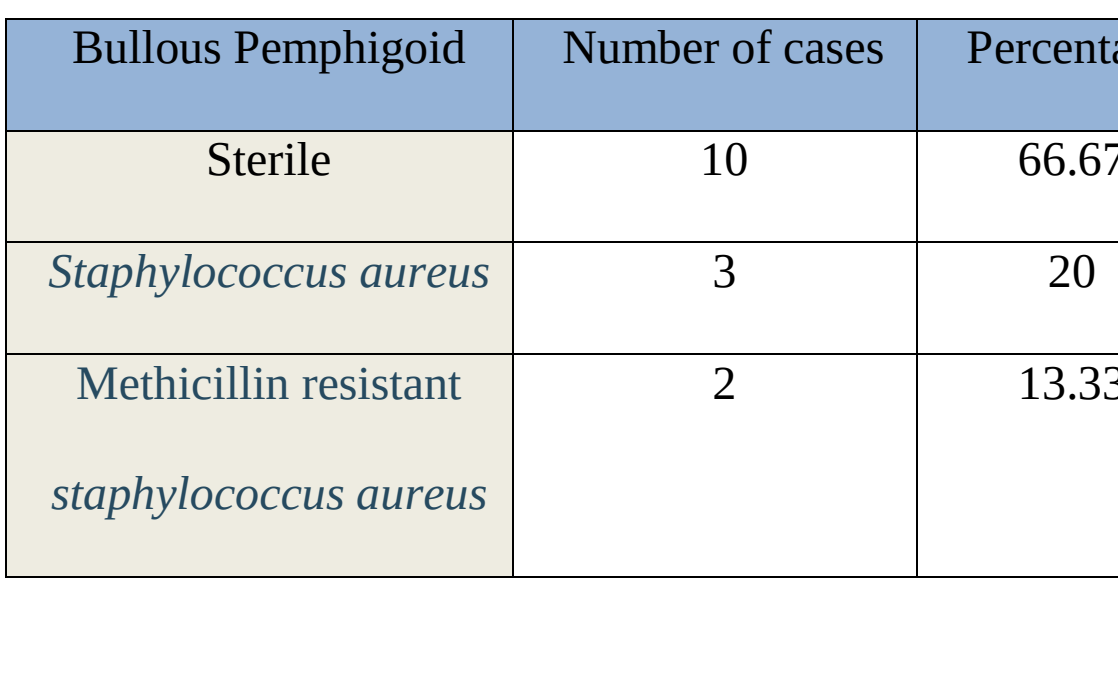


Figure 9: Microorganism isolated from lesions in Bullous Pemphigoid:

Microorganisms isolated from lesions across various group of AIBDs

In the Pemphigus foliaceus, Pemphigus vulgaris bacterial growth outnumbered sterile swabs; in contrast, a higher number of Bullous pemphigoid patients showed no growth as illustrated in table 14 and figure 10.

Table 14: **Microorganisms isolated from lesions across various group of AIBDs**

Disease	Pus culture						
	Sterile	SA	MRSA	CONS	SE	KP	PA
BP	10	3	2				
PV	29	8	5	2	1	1	2
PF	8	7	3				

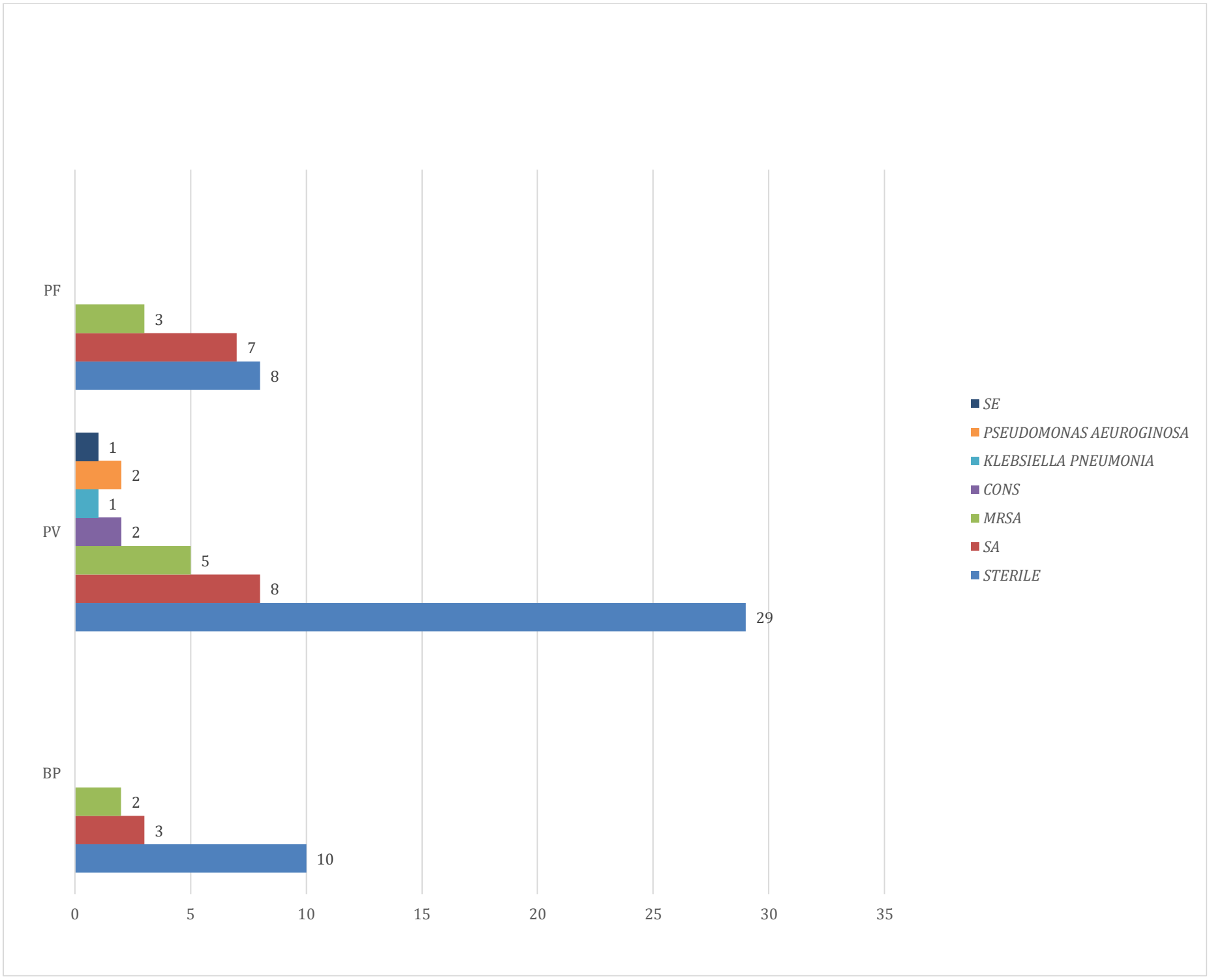


Figure 10: Microorganisms isolated from lesions across various group of AIBDs

Antibiotics sensitivity and resistance pattern *Staphylococcus aureus*

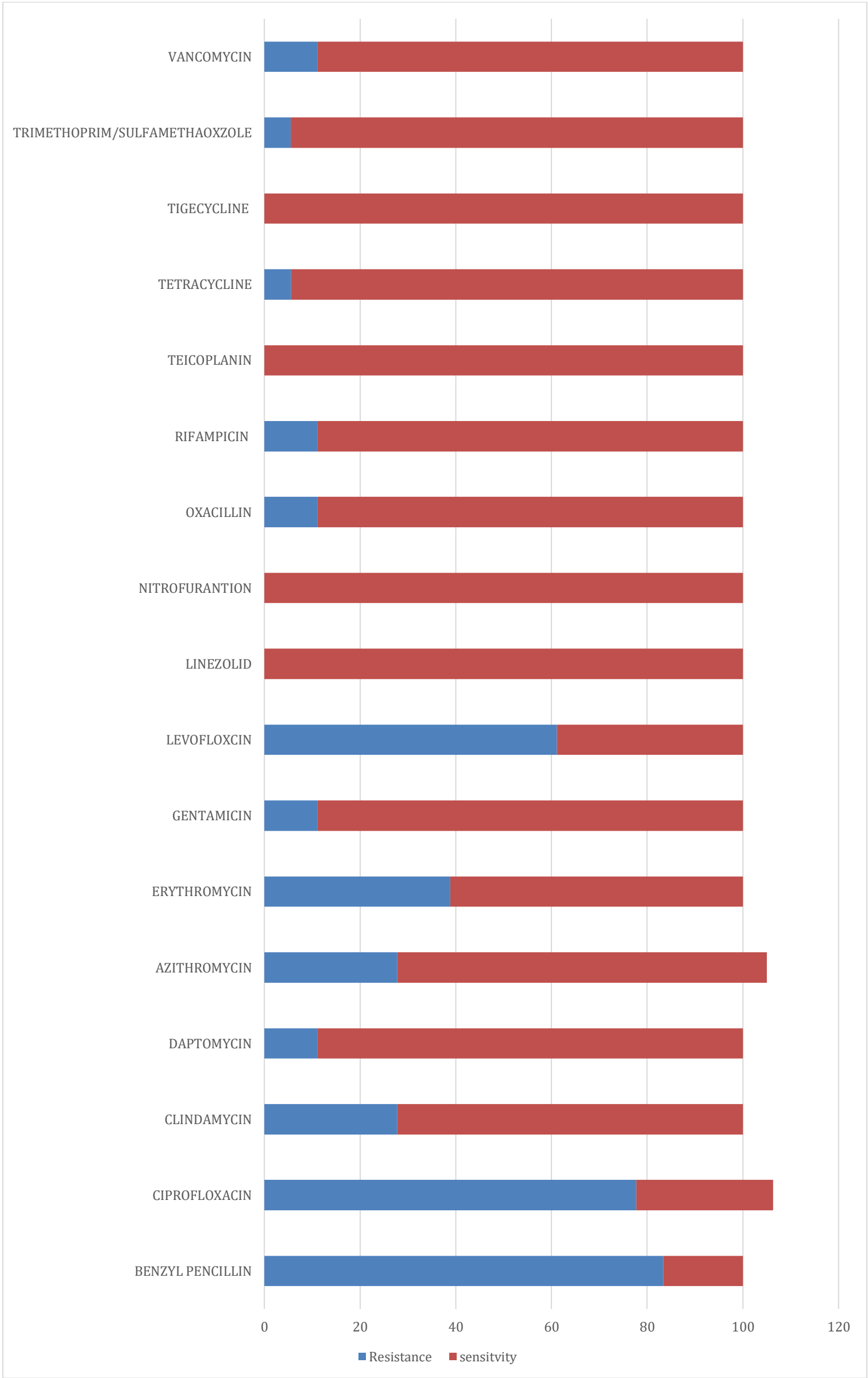
Antibiotics teicoplanin (100%), linezolid (100%), nitrofurantoin (100%), vancomycin (100%), tigecycline (100%) showed the highest sensitivity, followed by trimethoprim/sulfamethoxazole (94.44%), rifampicin (88.89%), oxacillin (88.89%), daptomycin (88.89%) and azithromycin (77.27%), as shown in table 16 and figure 16.

Benzyl Penicillin (83.33%) was the most resistant antibiotic, followed by ciprofloxacin (77.77%), levofloxacin (61.11%), and erythromycin (38.88%).

Table 15: **Antibiotics sensitivity and resistance pattern of *Staphylococcus aureus***

ANTIBIOTICS	SENSTIVITY		RESISTANCE	
	FREQUENCY	PERCENTAGE	FREQUENCY	PERCENTAGE
Benzyl penicillin	3	16.66	15	83.33
Ciprofloxacin	4	28.57	14	77.77
Clindamycin	13	72.22	5	27.77
Daptomycin	16	88.89	2	11.11
Azithromycin	13	77.27	5	27.77
Erythromycin	11	61.11	7	38.88
Gentamicin	16	88.88	2	11.11
Levofloxacin	7	38.88	11	61.11
Linezolid	18	100		
Nitrofurantoin	18	100		
Oxacillin	16	88.89	2	11.11
Rifampicin	16	88.89	2	11.11
Teicoplanin	18	100		
Tetracycline	17	94.49	1	5.56
Tigecycline	18	100		
Trimethoprim/sulfa methoxazole	17	94.44	1	5.55
Vancomycin	16	`100	2	11.11

Figure 11: Antibiotics sensitivity and resistance pattern of *Staphylococcus aureus*



Few antibiotics like Colistin, Amikacin, Cefoperazone +sulbactam showed sensitivity and resistance in only two cases hence they are grouped separately

TABLE: 16: Other Antibiotics sensitivity and resistance pattern

ANTIBIOTICS	SENSTIVITY		RESISTANCE	
	FREQUENCY	PERCENTAGE	FREQUENCY	PERCENTAGE
Colistin	3	100		
Amikacin	2	100		
Cefoperazone +sulbactam	2	100		
Cefuroxime axetil	1	100		
Ertapenem	1	100		
Imipenem	1	50	1	50
Meropenem	2	100		
Piperacillin / tazobactam	1	100		
Amoxicillin clavulanic acid	1	100		

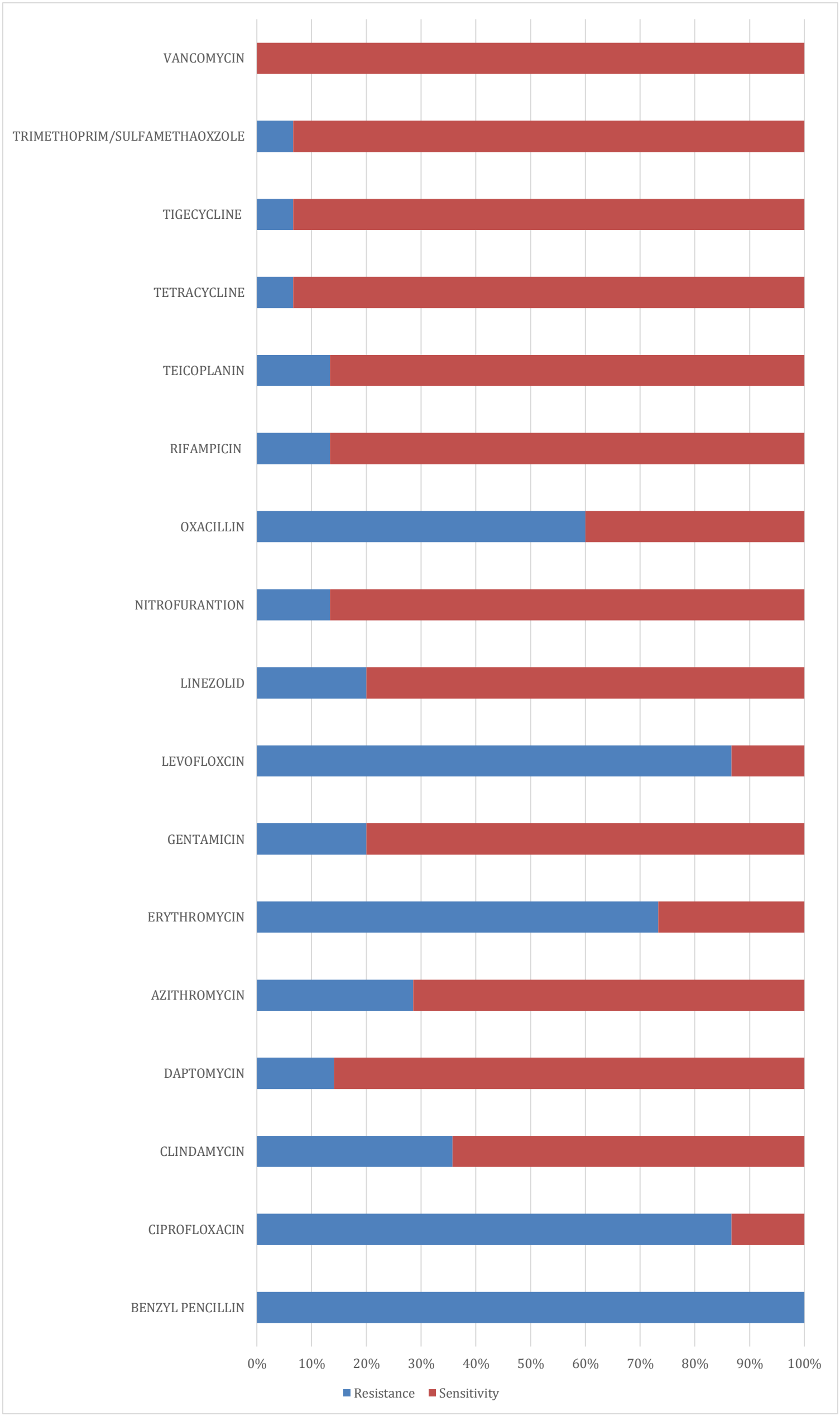
Antibiotics sensitivity and resistance pattern of Methicillin Resistant *Staphylococcus aureus*

Antibiotics are depicted in Table 17 and Figure 15 below. The maximum sensitivity was seen for Vancomycin (100%) and was followed by Tetracycline (93.33%), Tigecycline (93.33%), Trimethoprim/Sulfamethoxazole (93.33%), Nitrofurantoin (86.67%), Rifampicin (86.66%), Oxacillin (86.66.%), and Daptomycin (81.42-2.6%). Benzyl Penicillin (100%) was the most resistant antibiotic, followed by Ciprofloxacin (86.777%), Levofloxacin (86.67%), and Erythromycin (73.88%).

Table 17: Antibiotics sensitivity and resistance pattern of Methicillin resistant *Staphylococcus aureus*

ANTIBIOTICS	SENSTIVITY		RESISTANCE	
	FREQUENCY	PERCENTAGE	FREQUENCY	PERCENTAGE
Benzyl penicillin			15	100
Ciprofloxacin	2	13.33	13	86.66
Clindamycin	9	60	5	33.33
Daptomycin	9	81.42	2	13.33
Azithromycin	9	71.42	2	28.57
Erythromycin	5	26.67	11	73.33
Gentamicin	4	80	3	20
Levofloxacin	12	13.3	13	86.67
Linezolid	2	80	3	20
Nitrofurantoin	12	86.67	2	13.33
Oxacillin	13	86.66	9	69.2
Rifampicin	6	86.66	2	13.33
Teicoplanin	13	86.66	2	13.33
Tetracycline	14	93.33	1	6.66
Tigecycline	14	93.33	1	6.66
Trimethoprim/sulfa methoxazole	14	93.33	1	6.66
Vancomycin	15	100		

Figure 15: Antibiotics sensitivity and resistance pattern Methicillin resistant *Staphylococcus aureus*



DISCUSSION

Septicemia and superficial bacterial skin infections are the primary causes of death and morbidity in cases with Abids'. Systematic study needs to be conducted on a regular basis due to evolving bacteriological profile and antibiotic sensitivity patterns. The rising threat of antimicrobial resistance makes patients more prone to bacterial infections.[49]

To date, studies about determining the bacteriological profile and the antibiotic sensitivity patterns of cutaneous lesions in immunobullous disorders are lacking except for a few (4 in number) studies in the literature focusing solely on pemphigus vulgaris or bullous pemphigoid and other groups of AIBDs were not included.

In our study, we found pemphigus vulgaris (56.2%) to be the most common condition, followed by pemphigus foliaceus, and this finding is in accordance with other regional and international studies.[47,49,58,59]

.

The male-to-female ratio in our study was 0.77, which differed from previous studies.[47,49,60]Male cases (45.25%) were outnumbered by female cases (54.4%).

The swab taken for pus culture and sensitivity from the active cutaneous lesions showed sterility in 52.9% of cases, much higher than 15.15% of Bharubiya et al. and 18.36% of Kiran et al.

Bacterial growth was seen in 47.1 % of cases, and the most common organism cultured is *Staphylococcus aureus (45%),* which is much lower compared to Chauhan et al. (65.2%), Solanki *et al*. (72%), Qadim *et al*. (83.9%) and Esmail *et al. (93.7%).* But similar to (40.81%) Kiran et al. and Barbhuiya et al. (45.3%). 47,29.60.61,62,63

In this study (4.16%%), Kiran et al. (12.24%) and Chauhan et al. (17.89%) noted that *P. aeruginosa* was the second most common organism following *S. aureus.*

Out of sixteen *Staphylococcus*-positive swabs, eight were *Staphylococcus aureus*, one was *Staphylococcus epidermidis*, two were coagulase-negative *Staphylococcus*, and five had methicillin resistance.

Among forty-eight pemphigus vulgaris patients, 39.86% were non-sterile, and 60.14% were sterile, whereas, in eighteen pemphigus foliaceus patients, 55.56% showed growth, and 44.44% were sterile. In bullous pemphigoid cases, the number of sterile swabs (66.67%) outnumbered the bacterial growth (33.33%). Pemphigus foliaceous cases had the highest growth of bacteria compared to Pemphigus vulgaris and Bullous Pemphigoid.

In this study, *S. aureus* isolated from AIBD patients showed 100% sensitivity to teicoplanin, linezolid, nitrofurantoin, vancomycin, and tigecycline, while 89% sensitivity to rifampicin and 95% sensitivity to trimethoprim/sulfamethoxazole was observed. Solanki et al. found that S. aureus showed 100% sensitivity to cloxacillin, cefotaxime, and lincomycin, whereas Kiran et al. reported the highest sensitivity to tetracycline, amikacin, chloramphenicol, and netilmicin.

Staphylococcus aureus was resistant to benzylpenicillin (83.33%), followed by ciprofloxacin (77.77%) and levofloxacin (61.11%). Barbhuiya et al. noted that S. aureus had 90% and 80% resistance to benzylpenicillin and levofloxacin, respectively. This finding is consistent with our results, but Barbhuiya et al. showed higher resistance to the penicillin class of antibiotics. Comparable results were reported by Chauhan et al. and Kiran et al., who found that *S. aureus* was highly resistant to ciprofloxacin (55%) and co-trimoxazole (79%) and highly resistant to penicillin (90%), erythromycin (55%), and ciprofloxacin (55%) respectively.

The sensitivity pattern for MRSA to vancomycin was 100%, followed by tetracycline (93.33%), tigecycline (93.33%), trimethoprim/sulfamethoxazole (93.33%) and nitrofurantoin (86.67%). Antibiotics that were most resistant to MRSA were benzylpenicillin (100%) and then ciprofloxacin (86.777%), levofloxacin (86.67%), and erythromycin (73.88%).

Two swab culture isolates had *Pseudomonas aeruginosa*, which was sensitive to penicillins , lincosamides , macrolides, fluoroquinolones, tetracyclines and glycopeptide group of antibiotics as observed by Kiran et al., and one had *Klebsiella pneumoniae* was sensitive to carbapenem's, third generation cephalosporins and extended spectrum of penicillin group of antibiotics.

Limitations of this study include small sample size and there was no differentiation between infected and noninfected cutaneous lesions. Co-morbidities, other infection risk factors, and a prior antibiotic use history were not taken into account.

CONCLUSION

- In this study, we examined the bacteriological profile of active cutaneous lesions present in AIBDs and analysed the patterns of antibiotic sensitivity and resistance in the bacteria that were recovered.

1. Pemphigus vulgaris, pemphigus foliaceus and bullous pemphigoid were observed in 48(56.5%) ,18(21.2%) and 15 (17.6%) of the 85 patients with a diagnosis of AIBDs, respectively.
2. . The study included patients ranging in age from 0 to 85 years old. The most commonly affected groups were young adults in the 20–29 age range and older patients in the 60–69 age range, with a bimodal distribution
3. Females outnumbered males by a ratio of 0:0.77.
4. The percentage of non-sterile swabs on pus culture and sensitivity was 47.1%, which was lower than the percentage on sterile swabs (54.5%).
5. The most common organism isolated was *Staphylococcus aureus* (92.25%) in which 37.5% was resistant to methicillin, followed by *Pseudomonas aeruginosa* (5%) and *Klebsiella pneumoniae* (2.5%)
6. Pemphigus foliaceus patients (55%) had the highest rate of bacterial growth, followed by pemphigus vulgaris (39.86%) and bullous Pemphigoid patients (33.33%).
7. The majority of bullous Pemphigoid cases (66.67%) had sterile pus cultures, which were subsequently followed by pemphigus foliaceus (45%) and Pemphigus vulgaris (63.14%).
8. *Staphylococcus aureus* was 100 % sensitive to antibiotics teicoplanin, linezolid, nitrofurantoin, vancomycin, tigecycline, followed by trimethoprim/sulfamethoxazole (94.44%), rifampicin (88.89%), oxacillin (88.89%), daptomycin (88.89%) and azithromycin (77.27%).
9. The most resistant antibiotic to *Staphylococcus aureus* was benzyl penicillin (83.33%), which was followed by erythromycin (38.88%), ciprofloxacin (77.77%), and levofloxacin (61.11%).
10. The sensitivity pattern for MRSA to vancomycin was 100% followed by tetracycline (93.33%), tigecycline (93.33%), trimethoprim/sulfamethoxazole (93.33%) and nitrofurantoin (86.67%).
11. The antibiotics with the highest MRSA resistance were erythromycin (73.88%), ciprofloxacin (86.777%), levofloxacin (86.67%), and benzyl penicillin (100%).

12. *Pseudomonas aeruginosa and Klebsiella pneumoniae* were the least common organisms and were susceptible to penicillin's, lincosamides, macrolides, fluoroquinolones, tetracyclines and glycopeptide group of antibiotics.

SUMMARY

A hospital-based, prospective cross-sectional study was conducted from September 2022 to June 2024 to analyse the bacteriological profile of active cutaneous skin lesions in AIBDs and evaluate the antibiotic sensitivity and resistance patterns.

The salient features found in this study are listed below:

1. Pemphigus vulgaris was most prevalent AIBDs
2. There were bimodal age distributions among cases.
3. Females were more in number than males.
4. The number of sterile swabs was more than the non-sterile swabs.
5. Pemphigus foliaceus cases showed the highest bacterial growth.
6. Bullous pemphigoid had a maximum number of sterile swabs.
7. Staphylococcus aureus was the most organism isolated, and it was 100 % sensitive to teicoplanin, linezolid, nitrofurantoin, vancomycin, tigecycline and resistant to benzylpenicillin (83%)
8. Among S. aureus, 37.5% are resistant to methicillin (MRSA), and it was sensitive to vancomycin (100%) and resistant to benzylpenicillin (100%)
9. The least common organisms were Pseudomonas aeruginosa and Klebsiella penumoniae

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ETHICAL CLEARANCE CERTIFICATE

BLDE
(DEEMED TO BE UNIVERSITY)
Declared as Deemed to be University u/s 3 of UGC Act, 1956
Accredited with 'A' Grade by NAAC (Cycle-2)
The Constituent College
SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

BLDE (DU)/IEC/ 698/2022-23

30/8/2022

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Friday, 26th August, 2022 at 3.30 p.m. in the Department of Pharmacology** scrutinizes the Synopsis of Post Graduate Student of BLDE (DU)'s Shri B.M.Patil Medical College Hospital & Research Centre from ethical clearance point of view. After scrutiny, the following original/ corrected and revised version synopsis of the thesis/ research projects has been accorded ethical clearance.

TITLE: "A PROSPECTIVE CROSS-SECTIONAL STUDY TO DETERMINE THE BACTERIOLOGICAL PROFILE AND ANTIBIOTIC SENSITIVITY PATTERNS OF THE CUTANEOUS LESIONS IN IMMUNOBULLOUS DISORDERS".

NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR: Dr. Mayuri B. M.

NAME OF THE GUIDE: Dr. Ajit B. Janagond, Associate professor, Dept. of Dermatology.

Dr. Santoshkumar Jeevangi
Chairperson
IEC, BLDE (DU),
VIJAYAPURA
Chairman,
Institutional Ethical Committee,
BLDE (Deemed to be University)

Dr.Akram A. Naikwadi
Member Secretary
IEC, BLDE (DU),
VIJAYAPURA
MEMBER SECRETARY
Institutional Ethics Committee
BLDE (Deemed to be University)
Vijayapura-586103, Karnataka

Following documents were placed before Ethical Committee for Scrutinization

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

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CONSENT FORM

B.L.D.E (Deemed to be university) SHRI B.M PATIL MEDICAL COLLEGE

HOSPITAL AND RESEARCH CENTRE, VIJAYAPURA-586 103

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

TITLE OF THE PROJECT: -A Prospective cross-sectional study to the bacteriological profile and antibiotic sensitivity patterns of cutaneous lesions in immunobullous disorders.

PG GUIDE DR. AJIT B JANAGOND

PG STUDENT: DR. MAYURI B M

PURPOSE OF RESEARCH:

- To identify bacteriological profile in cutaneous lesions in immunobullous disorders

BENEFITS:

- Appropriate usage of antibiotics as per susceptible organism

PROCEDURE:

I understand that relevant history will be taken, and I will undergo a detailed cutaneous examination. I will allow the investigator to collect pus swabs from skin lesions.

RISK AND DISCOMFORTS:

I understand there is no risk involved, and I will experience no discomfort during the clinical examination.

CONFIDENTIALITY:

I understand that medical information produced by this study will become a part of my hospital records and will be subjected to the confidentiality and privacy regulation of the said hospital. Information of a sensitive personal nature will not be a part of the medical records but will be stored in the investigator's research file. If the data are used for publication in the medical literature or for teaching purposes, no names will be used, and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand I may see the photographs, and videotapes and hear the audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time concerned. DR. MAYURI B M is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which may influence my continued participation.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary, and I may refuse to participate or may withdraw consent and discontinue participation in this study at any time without prejudice. I also understand that Dr MAYURI B M, may terminate my participation in this study at any time after he has explained the reasons for doing so and has helped arrange for my continued care by my own physician if this is appropriate.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, and if such injury were reported promptly, then medical treatment will be available to me, but no further compensation will be provided. I understand that by my agreement for my participation in this study, I am not waiving any of my legal rights.

I have explained to (patient's / relevant guardian's name) the purpose of the research, the procedures required, and the possible risks and benefits to the best of my ability in the patient's own language.

_____ _____

Investigator / P. G. Guide Date

I confirm that Dr Mayuri B M has explained to me the research, the study procedures that I undergo, and the possible risks and discomforts as well as benefits that I may experience. I have read, and understand this consent form. Therefore, I agree to give my consent for my participation as a subject in this research project.

_____ _____

Participant / guardian Date

_____ _____

Witness to signature Date

B.L.D.E. U'S SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE,

VIJAYAPURA.

Department of Dermatology, Venereology and Leprosy.

PROFORMA

SCHEME OF CASE TAKING

1. General information

Name: SL no:

Age:

Sex: Address:

Contact no.:

Patient ID: Date:

2. History:

- General Physical Examination:

Weight: Pallor: Icterus: Cyanosis:

PR: Edema: Clubbing:

BP: Lymphadenopathy:

- Cutaneous Examination

- Systemic Examination

Cardiovascular system

Respiratory system

Central nervous system

Abdominal examination

Diagnosis:

Micro-organism cultured:

Sensitive Antibiotics:

Resistant Antibiotics

KEY TO MASTER CHART

F- Female, M- Male

R – resistant

S -Sensitive

PV – Pemphigus Vulgaris

NPV – Neonatal Pemphigus Vulgaris

PF – Pemphigus Foliaceus

BP – Bullous Pemphigoid

EBA – Epidermolysis Bullosa Acquista

LABD – Linear IGA bullosa dermatosis

SA- *Staphylococcus aureus*

MRSA – Methicillin resistant Staphylococcus aureus

SE – Staphylococcus epidermis

PA – Pseudomonas Aeruginosa

KP – Klebsiella pneumoniae

MASTERCHART

SL NO	NAME	AGE (YEARS)	SEX	DIAGNOSIS	MICRO-ORGANISM	ANTIBIOTICS																												
						BENZYL PENCILLIN	CIPROFLOXACIN	CLINDAMYCIN	DAPTOMYCIN	AZITHROMYCIN	ERYTHROMYCIN	GENTAMICIN	LEVOFLOXCIN	LINEZOLID	NITROFURANTION	OXACILLIN	RIFAMPICIN	TEICOPLANIN	TETRACYCLINE	TIGECYCLINE	TRIMETHOPRIM/SULFAMETHAOXZOLE	VANCOMYCIN	COLISTIN	AMIKACIN	CEFOPERAZONE +SULBACTAM	CEFUROXIME AXETIL	CEFUROXIME	ERTAPENEM	IMPENEM	MEROPENEM	PIPERACILLIN / TAZOBACTAM	AMOXCILLIN CLAVULINIC ACID
1	Shaila jadhav	48	F	PF	SA	R	S	S	S	R	S	S	R	S	S	S	S	S	S	S	S	R												
2	Firam kachapur	61	F	PV	SA	S	S	S	S	R	S	S	R	S	S	S	S	S	S	S	S	S												
3	Anil appasahebk oganur	29	M	PF	NIL																													
4	Mahadevi salodagi	35	F	PV	NIL																													
5	Siddaramk araveer	52	M	PF	SA	R	R	R	S	S	R	I	R	S	S	R	R	S	S	S	S	S												
6	Mahipati pundalik	60	M	BP	SA	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S												
7	Bhimarays oragappa	43	M	PV	CONS	R	R	R	S	S	S	S		S	S	R	S	S	S	S	S	S												
8	Laxmibai pintu pujari	26	F	PV	NIL																													
9	Kantamma gunnapur	80	F	EBA	MRSA	R	R	R	S	R	R	S	R	S	S	R	R	R	S	S	R	S												
10	Madivallap pa s kumbhar	42	M	PV	SA	R	R	S	S	S	S	S	R	S	S	R	S	S	S	S	S	S												
11	Altaf khalifa	35	M	PV	NIL																													
12	Sajanbeeab dulgani	50	F	PV	NIL																													
13	Shreedevi murgod	46	F	PV	SA	R	R	S	S	S	I	S	R	S	S	S	S	S	S	S	S	S												
14	Bhojumano har	62	M	PF	MRSA	R	S	R	S	S	S	S	S	S	S	R	S	S	S	S	S	S												
15	Pooja duragappa	27	F	PV	NIL																													
16	Bibayesha magrabi	60	F	BP	NIL																													
17	Shilpa hanamantra y	26	F	PV	NIL																													
18	Surekha	33	F	BP	SA	R	R	S	S	S	S	R	R	S	S	S	S	S	S	S	S	S												
19	Firam kachapur	61	F	PV	MRSA	R	R	S	S	S	R	R	R	S	S	R	S	S	S	S	S	S												
20	Anil appasahebk oganur	29	M	PF	SA	R		S					S		S				R			R												
21	Siddamma navani	62	F	BP	NIL																													
22	Hamida banu	52	F	PV	NIL																													
23	Surekha	33	F	PV	MRSA	R	R	R	R	S	S	R	R	S	S	S	S	S	S	S	S	S												
24	Ajith dilipkumar	18	M	PV	MRSA	R	S	R	S	S	R	S	S	S	R	R	R	S	R	S	S	S												
25	Shredevi r policepatil	28	F	PV	SA	R	I	S	S	S	R	S	S	S	S	S	R	S	S	S	S	S												

26	Gangadharbaslingappa	65	M	PF	SA	R	R	S	S	S	S	S	R	S	S	S	S	S	S	S	S	S												
27	Apoorva	19	F	PV	SA	R	R	R	S	S	R	S	R	S	S	S	S	S	S	S	S	S												
28	Laxmi sunilsonnad	28	F	PV	PA	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	I											
29	B/o laxmisunilsoonad	0.027 4	F	NPV	MRSA	R	R	R	S	S	R	S	R	R	S	R	S	S	S	S	S	S												
30	Shantabai	76	F	BP	MRSA	R	R	S	S	0	R	S	R	S	S	S	S	S	S	S	S	S												
31	Sharada	61	F	PV	KP		I					I											I	S	S	S	S	S	S	S	S	S	S
32	Ramzanbee	26	F	PV	PA		R					S											I	S	S				R	S	I		
33	Nilamma	42	F	PV	MRSA	R	R	S			R	S	R	S	S	R	S	S	S	S	S	S												
34	Dundappa madivalappa	52	M	PV	NIL																													
35	Namdev	45	M	PF	SA	R	R	R	S	R	S	R	S	S	S	S	S	S	S	S	S	S												
36	Sidaram	58	M	PF	MRSA	R	R		S		S		R	S	S	R	S	S	S	S	S													
37	Rajeshree	38	F	PV	NIL																													
38	Abdul basha razak	37	M	PV	CONS	R	S	S			R	S	S	S	S				S			S												
39	Banu	52	F	PV	NIL																													
40	Padmavati	85	F	PV	CONS	R	R	S	S		S	S	R	S	S	S	S	S	S	S	S	S												
41	Saherabanu	85	F	BP	SA	R	R	S			R	S	R	S	S	S	S	S	S	S	R	S												
42	Meenakshi	27	F	PF	NIL																													
43	Shahanaj	45	F	PV	NIL																													
44	Jyoti	40	F	PF	MRSA	R	R	R	S		R	I	R	S	S	R	S	S	S	S	S	S												
45	Parvati	63	F	BP	NIL																													
46	Mallappakumbar	63	M	BP	NIL																													
47	Ganga mahadevappa	39	F	EBA	NIL																													
48	Rajeshteesharad	38	F	PF	NIL																													
49	Laxmibai meti	62	F	BP	NIL																													
50	Nkjanvekar	85	M	BP	NIL																													
51	Prashuram yallappa	43	M	PF	NIL																													
52	Basawaraj mallappa	67	M	BP	NIL																													
53	Mahadev	20	M	PV	NIL																													
54	Tippabai	55	F	PV	NIL																													
55	Basvantmadar	55	M	PF	SA	R	R	S			S	S	R	S	S		S	S	S	S	S	S												
56	Basappalaxmanbagi	60	M	PV	SA	R	R	S			S	S	R	S	S		S	S	S	S	S	S												
57	Ramesh	40	M	PV	SE	R	R	S	S		R	I	R	S	S	R	S	S	R	S	R	S												
58	Indra bai	61	F	PV	NIL																													

59	Murtaza khadri	76	M	BP	NIL																												
60	Mahadev	20	M	PV	NIL																												
61	Shrikant	46	M	PV	NIL																												
62	Naveen rolli	19	M	PV	NIL																												
63	Meenakshi rathod	48	F	PV	NIL																												
64	Geeta belagi	32	F	PV	NIL																												
65	Vittal	65	M	PF	NIL																												
66	Meenakshi bevanur	27	F	PF	SA	S	S	S		S	S	S	S	S	S	S	S	S	S	S	S	S											
67	Ramesh gagabhogi	38	M	LABD	MRSA	R	R	R			R	I	R	S	S	S	S	S	S	S	S	S											
68	Gamanabai	47	F	PF	NIL																												
69	Tejashwini	27	F	LABD	MRSA	R	R	S			R	S	R	S	S	S	S	S	S	S	S	S											
70	Husenbi	26	F	PV	NIL																												
71	Meenakshi	48	F	PV	NIL																												
72	Shashikala	36	F	PF	NIL																												
73	Indra bai	61	F	PV	MRSA	R	R	R			R	S	R	R	S	S	S	S	S	S	S	S											
74	Amol krishna	27	M	PV	NIL																												
75	Geeta	33	F	PV	SA	R	R	R	R	R	R	S	S	S	S	S	S	S	S	S	S	S											
76	Shrishail	42	M	BP	NIL																												
77	Vittal	65	M	PV	NIL																												
78	Ramesh gagabudi	39	M	BP	NIL																												
79	Mohmad mulla	38	M	PV	SA	R	R	R	R	R	S	S	S	S	S	S	S	S	S	S	S	S											
80	Naveem	39	M	PV	MRSA	R	R	S	S		S	I	R	S	S	R	S	R	S	R	S	S											
81	Basamma	70	F	PF	NIL																												
82	Tabasuma	45	F	PV	MRSA	R	R	R	R	R	R	R	R	R	R	S	S	S	S	S	S	S											
83	Gangalinga	26	M	PV	NIL																												
84	Ramesh	50	M	PV	NIL																												
85	Sagar	29	M	PV	NIL																												

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