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Epidemiology and Pathophysiology of Common Skin Diseases in West Africa: An Immunodermatological Framework

Osazomon Imarenezor

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Osazomon Imarenezor

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Approved:
Capstone Committee

Major Professor: Dr. Mir Saleem

Committee Member: Dr. Emily Schmitt

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HALMOS COLLEGE OF ARTS AND SCIENCES

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By

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I. Abstract

This capstone reviews the common skin diseases on a global scale. With these dermatoses being further funneled into Africa and then magnified into common West African dermatoses, the meta-analyses of literature available paints a clear picture of the epidemiological & pathological factors and their contribution to the skin disease. Each article analysed in this analysis was taken from a 20-year span of January 2000 to December 2019. The selection of articles was fine-tuned by identifying the distribution of skin disease, revealing the populations affected (age, gender, ethnicity, etc), the main causes, country of origin, the prognosis of disease, and the pathology of the specific skin condition. The top 15 common skin diseases of West-Africa ranked by count and relative frequency are Atopic Dermatitis (RF: 7.49%), Pityriasis (Tinea) Versicolor (RF: 4.94%), Acne Vulgaris (RF: 3.73%), Papular Urticaria (RF: 3.47%), Tinea (unspecified dermatophytosis) (RF: 2.94%), Contact Dermatitis (RF: 2.94%), Scabies (RF: 2.76%), Seborhheic Dermatitis (RF: 2.50%), Pityriasis Rosea (RF: 2.26%), Urticaria (2.18%), Human Pappilomavirus / Viral Warts (1.85%), Tinea Capitis (RF: 1.80%), Lichen Planus (1.77%), Vitiligo (RF: 1.77%) and Lichen Simplex Chronicus (RF: 1.45%). Moreover, each epidemiological and pathophysiological/pathological factor plays a role in skin disease, and unveiling the methods, such as potential immunotherapies and public health initiatives, to alleviate the burden of these dermatoses are at the forefront of continuing this research.

Key Words: ECOWAS, West Africa, skin, disease, dermatoses, epidemiology, pathophysiology, dermatologic, prevalence, cutaneous, incidence, immunology, Nigeria, Ghana, Benin, Cameroon, US, frequency.

II. Introduction

A. Skin's Role in Disease

The skin remains the largest organ at the barrier between the host and the outer world that provides the human body with the ultimate security to outside pathogens seeking infiltration. When these detrimental insults infiltrate this shielding, crucial tissue function is impaired. This impaired function leads to a plethora of diseases such as contact dermatitis, pityriasis versicolor, urticaria or atopic dermatitis. This compromised security in the skin now initiates the initial innate immune response, that is generally activated as a means to clear such atrocious microorganisms. This first response utilizes natural detection of the offensive patterns unique to these antigens, whether from the individual or foreign to the individual's repertoire of genetic material. Similar but slightly different is the next line of defense, the adaptive immune system. After the first attempt to clear the bacterium, virus or other pathogen, this robust family of proteins orchestrate a slower response to conclusively clear the tissue of the pathogen (Harris & Richmond, 2014).

When aberrancies arise in this area, there noticeably happens to be a slew of skin disorders that arise with the hiccups. Tumor immunity, allergic reactions, as well as autoimmunity are a few of the key players in the most common skin diseases that harass the globe. Respectively warts, allergic contact dermatitis, and vitiligo paired with lupus are only the tip of the iceberg of the phenotypic expressions of these immunodermatological adversaries (Richard & Harris, 2014).

Epidemiologically speaking, one can tie together genetic factors that bridge the alterations of the genome in relation to skin disease. Although the field of epigenetics is new, the epidemiology of skin disease potentially relates to the various stressors of skin disease such as stress, consistent exposure to pathogenic microorganisms, socioeconomic status, gender, age and more. This paper lightly reviews potential genes and their epigenetic contributions to West African skin disease, where literature is scares for this demographic.

B. Skin Disease Worldwide

The main pillar of this study is to unveil why skin diseases are important to study. Skin disease is the 4th leading cause of non-fatal disease burden worldwide. According to the skin experts in the Global Burden of Skin Diseases study in 2010, skin disease is additionally the 11th

leading cause of disease burden on the country level (Aksut, Dellavalle, & Naghavi, 2017). As the skin is the clinical representation of disease, it can be the secondary presentation of a general biological process, as these conditions are identified as sequelae of the aforementioned biological process. Other factors differ for varying regions surveyed, such as income level and type of climate, as covariates contributing to skin disease.

As children and their loved ones take on the short end of skin disease burden (Mahe, 2005), women are mostly affected by non-fatal skin disease. However, in terms of aging populations above 70 years, eczema, ulceration, non-melanoma skin cancer (NMSC), infections, and symptoms such as pruritus, are of major concern (Ghazizadeh, 2010). In most adults, eczema is the leading skin disease related to disability-adjusted life years. These populations and the diseases correlated to them must be closely examined as significant relationships can be translated to the affected demographic (Hay etl al., 2014).

C. Skin Disease in Africa

Delving deeper into skin diseases in Africa requires surveying a variety of epidemiological variables in regards to which skin diseases are the most common of the top global skin diseases. With these diseases in mind, this study will unveil the exact dermatoses that are also shared with the general African population. As Africa boasts of being one of the most populous continents, with it's 1.34 billion people as of 2020 and nearly double projected for 2025 at 2.53 billion. (U.S. Census Bureau, International Data Base, 2019.) being centered at the equator, skin disease in this continent is expected to differ from the rest of the globe.

The continent holds a highly tropical (hot, humid) climate with higher seasonal levels of UVA and UVB rays. This environment allows for higher production of Vitamin D as well as natural selection of individuals with a genetic pool more inclined to pigmentation of the skin (Kagotho et al., 2018). This may give reason to the higher concentration of auto-immune diseases of pigmented skin, such as vitiligo, one of the top 15 skin diseases that affect primarily West Africa. The World Health Organization has shown that this climate, access to clean water with poor hygiene, close quartered-living, and insect-bites are prime etiological factors of overall detrimental dermatoses in 3rd world countries (MacDonald, 2005).

With the majority of African countries being developing nations, this study seeks to elucidate the factors that have made the aforementioned dermatoses among the most common

skin disorders in sub-Saharan Africa. Factors such as fairly high amounts of overcrowding in homes, communal use of bedding in poor housing conditions, illiteracy, hygiene contribute to the disorder. Scabies is known as the 'communal' disease as it directly results from such conditions in close-quartered communities (Hay et al, 2012). Similar to the global findings, the population most susceptible to these skin conditions in Africa are children as well. This review article will shed light on susceptible demographics to skin diseases in Africa. Unearthing these dermatoses is weighed on the highly variant factors specific to each region (North, South, East, West, Central, and/or Sub-Saharan). These factors include, but are not limited to, geographic location, climate, socioeconomic privilege, and epigenetics. To extend further, the continent's lack of burden awareness contributes to the root of the derm issues (Ugbomoiko et al, 2018).

D. Skin Disease in West Africa

West Africa is comprised of 15 countries: Benin, Burkina Faso, Cape Verde, Cote D'Ivoire, Gambia, Ghana, Guinea, Guinea Bissau, Liberia, Mali, Niger, Nigeria, Senegal, Sierra Leone, and Togo (2016, ECOWAS). The largest city and country in Africa lies directly in West Africa: Lagos, Nigeria. On the other hand, with large populations come large responsibility as the access to stable housing (i.e. no overcrowding housing arrangements), clean water, pollutant-free air, and adequate health care are fundamental in mitigating the pathogenesis of these dermatoses. This capstone research will look closely at skin diseases in West Africa, particularly in Ghana and Nigeria. For example, in Nigeria, skin disease manifests differently for those in Northern and Southern regions by matters of inflammatory and infections/infestations versus cosmetic-related dermatoses, respectively (Henshaw et al., 2018).

As far as skin disesase in Africa, we have varying dermatoses that traverse across the respective regions of Africa. The large continent boasts significantly different epidemiological, genetic, environmental, and socioeconomic factors in the northern, southern, eastern, western, and central regions. For instance, in Egypt, there is an incidence of vitiligo at a rate of 2.2% (El-Khateeb, Imam, Sallam , 2011) , while the rate of incidence in Ghana (sub-saharan/West Africa) stands at a midly higher rate of 4.16% (Rosoenbaum et al., 2017). Although vitiligo has no known preference for race nor gender, this still attests to the multitude of diseases that vary across one of the largest continents and most diverse population on the planet.

West Africa has a steroid problem. Approximately 70% of Nigerian women bleach their skin. Unfortunately, most times, these creams utilized are highly caustic and relatively corrosive. With common ingredients such as mercury, steroids and high levels of hydroquinone, these creams can lead to major problems with cause major skin irritation and thinning, acne, blisters and dangerous chemical burns. At this level of melanin degradation occurring, it can prove to be debilitating. Future side effects can possibly include aggressive forms of skin cancer including breast cancer, melanoma and possibly merkel cell carcinoma (Brinton, et al., 2018).

III. Immunology of the Skin

A. Epidermis: Frontline of Protection

The skin is comprised of two major layers: the epidermis and the dermis, with the underlying subcutaneous layer frequently studied simultaneously (see figure below).

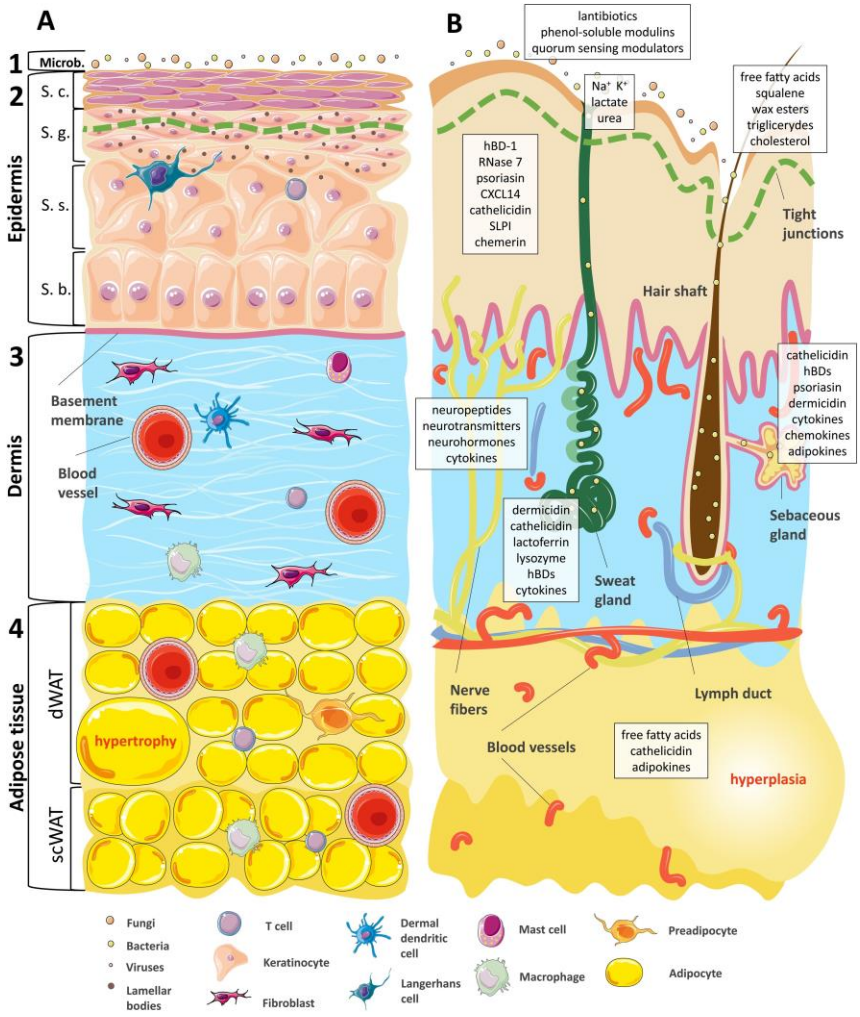


Figure A: Subcutaneous, Dermal and Epidermal layers of the skin against their respective dermatoimmune counterparts. Figure B: Additional biological systems of the skin. (Kwiecien, et. al (2019).

Within this triad, there are four structural sections of the epidermis that encompass these layers: the stratum basale or basal membrane, stratum spinosum, stratum granulosum, and stratum corneum (Bäsler, et al., 2016). There is also stratum lucedum in thick skin such as the hands and feet.

1. Stratum Basale

At the base of this 0.1mm thick layer (Chambers & Vukmanovic-Stejic, 2019) is the stratum basale, which is comprised of stem cell- like cells, which differentiate into keratinocytes, the most populous cells In the epidermis. These epidermal-resident tissue cells are replenished throughout the four layers of the epidermis. As they are stationed in the basal layer, this monolayer of cells then differentiates apically. Furthermore, specialized cells that reside in the epidermis are melanin-shuttling melanocytes that attach to the basal layer and are interspersed throughout the epidermis on the border of the dermal-epidermal junction (DEJ) (Yamaguchi, Brenner, & Hearing 2007); these cells protect against UV-radiation through pigment expression (Chambers & Vukmanovic-Stejic, 2019).

2. Stratum Spinosum

Once these basal keratinocytes traverse upward to the stratum spinosum (prickle cell layer, as some like to reference), a process called maturation initiates. The morphology of the keratinocytes in the stratum spinosum go from cuboidal to polygonal in order to process the keratins specific to the prickle cell layer. Langerhan cells, resident memory T cells and CD8+ T cells can be found throughout the stratum basale and the stratum spinosum (Nestle et al., 2009). Interruptions in keratinocyte differentiation and aberrant lipid composition in this layer of the skin gives rise to skin diseases such as atopic dermatitis and ichthyosis vulgaris. (Palmer et al., 2006, Smith et al., 2006)

3. Stratum Lucidum

The stratum lucidum is the layer of the skin 2-3 cells wide that is soley on the palms and soles with little to no hair in this area. This thick layer is comprised of eledin, the transformed version of keratohyalin (Yousef, Alhajj, &Sharma, 2020).

4. Stratum Granulosum

The stratum granulosum is the layer of the epidermis, two layers from the stratum basale. This layer has two types of granules: lamellated and keratohyalin. The majority of cell organelles are damaged, but the cell is still functional and alive. The 3-5 layers of cells contain keratin that aggregates, crosslinks and forms bundles to provide a polygonal and rectangular shape. Lamellar

bodies fuse both the stratum granulosum and the stratum corneum to create a continuous bilayer during simultaneous production of keratin proteins, lipids, and antimicrobial peptides (AMPs) that allow for the desquamation of cells at the stratum corneum (Yousef, Alhaj, & Sharma, 2020).

5. Stratum Corneum

As the keratinocytes flatten out, they then terminate themselves due to their pyknotic nuclei, thus these terminal cells of differentiated keratinocytes are void of organelles (Nestle et al., 2009). This comprises the stratum corneum. The corneocytes are key contributors of the barrier functionality of the stratum corneum by rejecting toxic proteins and arms the skin with a watertight barrier that prevents transepidermal water loss to the tissue (Brandner et al., 2014).

B. Epidermal Cells

1. Skin Stromal Cells

a. Keratinocytes

Keratinocytes are epidermal resident cells which express multiple pattern recognition receptors (PRRs) that detect arduous proteins with innate recognition patterns (PAMPS) to recruit diverse immune cell populations to battle and localize inflammatory response. The main PRRs for keratinocytes are more widely known as the toll-like receptors (TLRs) and nucleotide-oligomerization domain- like receptors (NLRs). Specific to these stratified cells, TLRs 1,2, 3, 4, 5, 6, 9 and 10 (Kollish et al., 2005,) which specifically bind to their respective linds to recruit antimicrobial organisms, or antimicrobial peptides (AMPs) to ward off pathogenic insults to the epidermis and maintain homeostasis of the skin microbiome. As the TLRs are grouped into two categories of cell surface (TLRs 1,2,4,5,6) and intracellular (TLRs 3,7,8,9) to recall emblems on bacteria, viruses, or fungi. TLR-10 is not ligand-specific yet, as researchers are still seeking to find its true partner. Each designated TLR recognizes patterns in microorganisms that are specific to the genetic instruction of the protein. (Klicznik, Szenes-Nagy, Campbell, & Gratz, 2018). These cell-specific membrane proteins induce NF-κB and interferon-regulatory factors, transcription factors that direct the creation of cytokines used to combat inflammation and type I interferons (IFNs), respectively (Kawamura, Ogawa, Aoki, & Shimada, 2014).

In addition to this cascade effect, the keratinocyte-specific TLR3, generates the cytokines interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα) which influence gene expression and keratinocyte proliferation, and barrier restoration (Borowski et al., 2013, Klicznik, Szenes-Nagy, Campbell, & Gratz, 2018). It has been established that IL-1α, IL-25, and IL-33 are stored strategically for rapid release in the presence of nearby proteases upon injury (Dickel et al., 2010). After a point of barrier infiltration is sensed, keratinocyte express chemokine ligands such as the CXCL20 and CCL27 to induce adaptive and innate immune responses (Kennedy-Crispin et al., 2012). These proteins then recruit and present to CD4+ T Cells and CD8+ T Cells though their compatible chemokine receptors CCR6 and CCR10.

b. Melanocytes

Melanocytes are the pigment carrying cells that reside in the epidermal-dermal junction (DEJ). Melanin is produced through these cells and also contributes to the innate immunity in regards to the vascular endothelial growth factor 165 (VEGF165) being upregulated in melanocytes through exposure to ultraviolet B . This increased expression of the VEGF ligand induced cell proliferation, in both normal melanocytes and under hypoxic and oxidative stress conditions, with an influx of cells undergoing melanogenesis (Zhu et al., 2020). This is the key cell destroyed in the autoimmune disorder vitiligo.

c.. Merkel cells (MCs)

Merkel cells (MCs) are the nerve cells of the skin which are heavily involved in the endocrine and nervous systems. In addition to the neuro-endocrine system they are important in mechanoreceptor and nociceptive responses. In immunity, MCs highly express the CD200 protein, which is crucial in inflamed environments as well as immunity tolerance. These cells produce the neuropeptide calcitonin-gene related peptide (CGRP), which can prevent Langerhan cells from presenting antigens within the epidermis. As intermediates of inflammatory mechanisms, stromatin, and the vasoactive intestinal peptide (VIP) are a few proteins secreted by MCs (Abraham & Mathew, 2019). In relation to skin disease, upregulation of MCs in psoriatic lesions are key indicators of this cell's crucial role in dermatoimmunology (Xiao, Williams, & Brownell, 2014).

2. Innate Immune Cell Demographics (Bone Marrow-Immune Cells)

Langerhan Cells

The epidermis is sporadically entangled with a main type of macrophage population such as the Langerhan Cells (LC's). Furthermore, these cells also have the capabilities to renew themselves (Hoeffel et al., 2012). Although LCs have been revealed previously to commit to induce tolerogenic responses and simultaneously responding to immunogenic signals and presenting immunogenic surface phenotypes (Shklovskaya, 2011), the cluster of differentiation transmembrane lectin receptor Langerin (CD207) is the standard trait for identification of Langerhan cells. These lectin proteins initiate the formation of Barbick granules, key markers in mouse and human epidermal tissue (Valladeau et al., 2000). Langerhans also express CD1a, CD11b, CD11c, with major histocompatibility complex II (MHC-II), and F4/80 surface protein to identify the immunophenotype of these cells (Guilliams et al., 2014). Upon recognition of a mannose-PAMP on a ligand antigen, the LC's CD207, langerin receptor forms a complex with CD1a and translocates an antigen through exocytosis, in the Birbeck granules. These antigens presenting epidermal-resident cells are strong dendritic players in immune responses of the skin, as this is their primary function (Tsepkolenko et al., 2019). Langerhans are able to express the matrix metalloproteinases (MMPs) that are essential to vasodilate blood vessels for them to extravasate through the basal membrane to reach the specific lymphatic pathways (Ratzinger et al., 2002). MMP-9 and MMP2 are the trafficking regulators in Langerhan cells as MMP-9 and MMP-2 deficient murine skin models showed alarming rates of inhibitory migration of LCs into the skin at rates of roughly 30-50%.(Ratzinger, 2002). From an immunological standpoint, LCs are crucial for the calling of T follicular (TFH) cells. Depletion of Langerhan cells, as recent studies have shown, decrease TFH cells by nearly roughly 50% in adaptive response during intradermal (ID) immunization while germinal center (GC) B cells were also reduced by nearly 60% (Levin, et al., 2017).

C. Dermis: Vascular Motherboard

While there is no blood supply in the epidermis, the inferior dermis layer is stationed with substantial amount of blood vessels, extracellular matrix proteins that house collagen, the connective tissues reticulin (the type III collagen fiber) & elastin, along with immune sentinels. These immune 'soldier-like' cells include dermal dendritic cells (dDCs), plasmacytoid dendritic

cells (pDCs), and the highly responsive T cell subsets: CD4+, T helper 1 (TH1), T helper 2 (TH2) and T helper 17 (TH17) cells, γδ T cells and natural killer T (NKT) cells. To champion these immune cells on are more inflammatory players such as dermal fibroblast cells (dFBs), macrophages and mast cells (Nestle et al., 2009). The first of two layers are the papillary and reticular layers that lie in the upper and lower areas of the dermis, respectively. The papillary layer supplies the epidermis with nutrients necessary to generate keratinocytes, while regulating the temperature of our skin and body. This layer provides the blood vessels and expels waste that would otherwise kill skin cells to aggregate. The reticular layer provides the skin with elasticity, which allows for our skin to bounce back into it's original form when interrupted. This deep layer includes hair follicles, sebaceous glands, and other sweat glands that are apart of apocrine or eccrine glands (Brown, 2018).

1. Active Cells

a. Fibroblasts

Dermal fibrolast cells are the substantial proteins throughout the vascular dermis layer in concert with dermal-resident stromal and immune leukocytes. These cells are readily accessible through vasodilated plasma vessels upon inflammatory response. As they are the warehouse of collagen, elastin, and other structural-cell production, they additionally initiate and amplify signal transduction during inflammation. These structural cells carry all TLRs 1-10 which is significantly higher than their expression of keratinocytes within the epidermis. For instance, activation of these TLR4 in the dermis results in a high-fold increase of cytokines induces IL-6, IL-8, indicating the supreme role of dermal fibroblasts in immune response (Cheng et al., 2015). Specifically, these fibroblasts express the cytokines interferon γ (INFγ), TNFα, IL-12p70 and IL-10. Of course, more extensively than the keratinocytes, the dermis secretes the chemokines CCL1, CCL2, CCL5 and the chemokine motif ligands CXCL1, CXCL8, CXCL10 and CX3CL1. Furthermore, the growth factors and growth factors granulocyte/macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) becoming stimulated upon fibroblast activation. On the other hand, these fibroblasts are also known to divert T-Cells to a IL-10 regulatory state through indolamine 2,3 dioxygenase production (Haniffa et al., 2007).

b. Endothelial cells

Endothelial cell populations are lined among the blood vessels of the dermis and have surface molecules that can detect and initiate a response from stimuli in the environment. As these PAMPs recognize foreign patterns, they elicit responses that resemble unique characteristics of traditional, innate immune cells. The unconventional endothelial and epithelial cells contain E and P selectin, Fc- receptors, proinflammatory cytokines such as TSLP, IL-33, and IL-25 (Roan, Obata-Ninomiya & Ziegler, 2019). These signals are sufficient in their tactics to behave as antigen presenting cells (APCs) to B and T cells throughout the skin (Mann et al., 2012).

When speaking about key players in the dermis, note that during inflammatory response, structural fibroblasts in the dermis differentiate into these dermal white adipose tissue cells and then secrete the AMP, cathelicidin Although fairly de novo, recent studies have shown AMPs roles in the skin, primarily involving their origin in the subcutaneous layer and the pilosebaceous glands. (Chen, Zhang, & Gallo, 2019).

c. Myeloid dermal dendritic cells

Myeloid dermal dendritic cells are the family of myeloid progenitor cells that eventually differentiate into mature dermal dendritic cells in the lymph. Once activated, these DC populations mature post-exposure to PRRs and drain to their localized (dermal) lymph nodes. Once these cells complete differentiation, the result is two specific sub-families of dendritic cells. The CD103+ with CD141+ and the CD1C+ and CD11b+ cells are the key myeloid dermal macrophages which initiate antigen presentation. Macrophages also express F4/80 and CD11b markers, but do not express the novel Langerhan cell markers, CD207 and CD11c. The lack of the MHC-II complex on these cell populations halts these cell's activity in the downstream activation of the adaptive immune response (Guilliams et al. 2014). When looking into skin disease, atopic dermatitis' immunology intimately involves the activity of myeloid dendritic cells. The chemokines CCL22 and CCL17 are released upon activation and recruit Th2 cell in the acute phase of this condition. (Kashem, Haniffa, & Kaplan, 2017).

d. Plasmacytoid dendritic cells (pDCs)

In relation to injury to the skin, recent studies have shown after 24 hours post-injury to murine skin, plasmacytoid dendritic cells' (pDC) presence parallels with upregulated mRNA gene expression of both IFN alpha-and beta (Gregoria et al., 2010). Additionally, the expressed

TLR7 and TLR9 are vital for immune responses. Guiducci and colleagues unveiled that treating pDCs with an oligonucleotide antagonist, blocked TLR 7 and TLR 9 expression and discovered this to significantly reduce fundamental inflammatory cytokines, including IFN-alpha. (Guiducci, 2010). Furthermore, downregulation of pDCs are directly correlated with downregulation of IL-6 and Th17 cytokines IL-22 and IL-17, indicating the necessity of these proteins in inflammatory conditions such as tape-stripped murine skin. IL-6 is a key cytokine involved in the keratinization of wounded skin that contributes to rebuilding the epidermis of the skin (Gallucci et al., 2004). As these cells are the primary immune cells in autoimmune disease, such as vitiligo, interactions with the heat shock protein 70 (Hsp70), create the prerequisite IFN-alpha in vitiligo patients (Jacquemin, et al., 2017).

e. Mononuclear Phagocytes

Within the skin, the mononuclear phagocytes are monocytes and macrophages that exist within circulation and tissues, respectively(Hoeffel et al, 2012; Knipper et al., 2015). Similar to the pDCs, these cells carry a wide range of the PRRs, TLRs, thus having the capabilities to detect key PAMPs within dermal inflammation. The previously mentioned LCs and dermal macrophages comprise the two major classes of macrophage demographics in the epidermis and the dermis, respectively. As we are familiar with the LCs, macrophages also carry the capacity to express the surface markers F4/80 and CD11b. However, they differ by their lack of expression of CD11c nor Langerin with lower MHC-II glycoprotein (Minutti, Knipper, & Allen, 2017). As aforementioned, we are familiar with LCs activity in injury and skin aberrancies, in reference to dermal macrophages, studies have identified this population of mononuclear phagocytes as the main source of VEGF in the vital process, angiogenesis, of early wound repair (Willenborg, et al., 2012).

f. Resident Macrophages

Resident macrophages are a distinct phagocytic cell that arise from the monocytes in the blood. These macrophages, called M1 cells, come about through collecting at the site of inflammation in response to injury (Mantovani et al., 2004). As these cells are also able to secrete various cytokine proteins for adequate function within the skin's innate immune response, they do also carry the PRR that allow them to behave as prominent phagocytes and bactericides. Upon their activation, the aforementioned cytokines initiate antigen processings,

along with phagocytosis that precedes the necessary growth factors (VEGF, KGF, etc) that are active in wound healing. The other resident macrophage family cells, the M2 macrophages are the primary sources of IL-10, to generate T-Helper 2 Cells (Th2 cells) (Gerber & Mosser, 2001). Recent studies that have reviewed how the skin utilizes resident macrophages during wound repair and secrete the cytokine IL-4. This released cytokine is used to organize the collagen fibrils post direct insult to the epidermis. Without this key cytokine available, the levels of lysyl hydroxylase2, (LH2), are lowered, thus stunting the necessary collagen cross-links that are needed during reconstruction of wounded skin (Knipper et al., 2015). With this in mind, the macrophages withhold the ability to generate fundamental molecules that mediate the production of the skin collagen's structural synthesis.

D. Hypodermis: Thermal Regulation and Anti-Microbial Protection

The hypodermis is primarily composed of adipocytes that serve to intentionally store fat to provide a multitude of advantageous services to the skin. These dermal white adipose tissue cells (dWATs) are essential in attenuating homeostatic capabilities of thermogenesis, by expansion in exposure to cold temperature. dWATs orchestrate defenses against microbial pathogens that give rise to bacterial infection, support adequate wound healing and champion healthy hair growth (Alexander et al., 2015). This essential layer has been elucidated in a murine study where dWATs expand in the presence of the bacterium Staphylococcus aureus, thus releasing the antimicrobial peptide cathelicidin, killing off the invasive bacteria (Zhang et al., 2015). This process, deemed reactive adipogenesis, takes place in the pilosebaceous gland adnexal to the hair follicle. In this process, as the dWATs take on a conical shape in the hypodermis, mature adipocytes generated from preadipocytes increase expression of (peroxisome proliferator-activated receptor γ) PPAR-γ and CEBP-α, to produce adipokines, a family of inflammatory cytokines (Zhang et al. 2018). Another study conducted noted that uncommitted embryonic cells to (the precursor cells of dWATs) aged adult dermal fibroblast cells(dFBs) are susceptible to transforming growth factor beta (TGF-β) pathway that inhibits adipogenic and antimicrobial activity (Zhang et al., 2018).

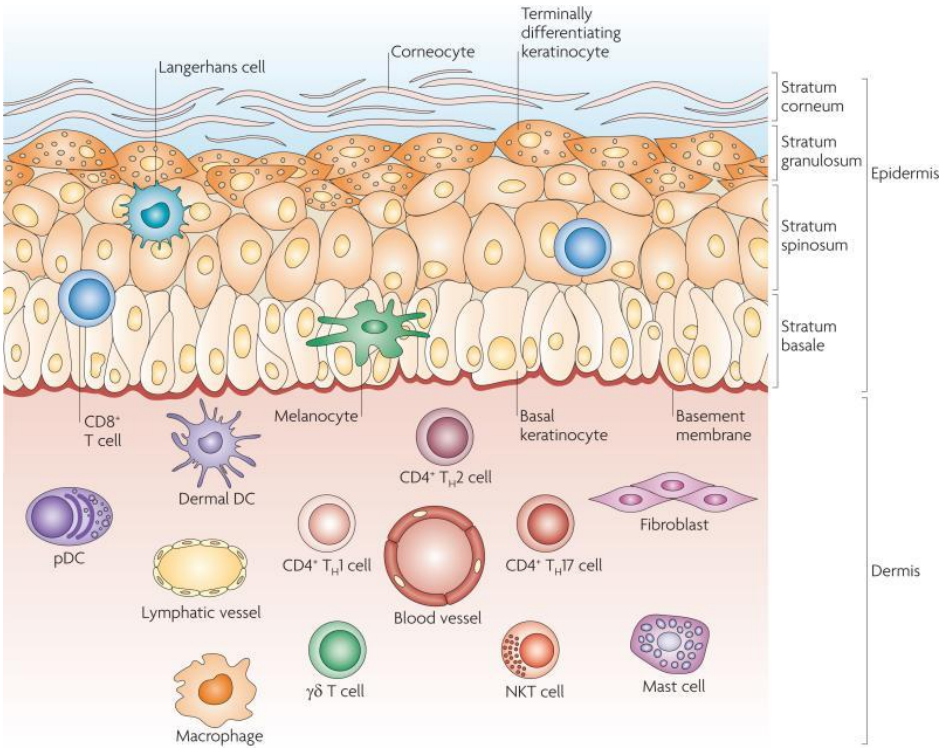


Figure B: Hierarchy of the cellular components of the skin. (Nestle et al., 2009)

E. Non-Specific Immune Cells

1. Granulocytes (polymorphonuclear cells)

a. Mast Cells

Mast cells are daughters to the precursor myeloid progenitor cells. These cells are grouped with resident immune cells which release granules upon activation during skin tissue injury (Cardamone et al., 2016, Igawa & Nardo, 2017). This release is initially done by excretion of histamines, including but not limited to, serotonin, heparin and a myriad of enzymes. This cell population is the key mediator of hypersensitivity environments (i.e., allergies). Their early stage cells, the mastocyte, are the producers of VEGF, FGF and the nerve growth factor (NGF)(Cardamone et al., 2016). Once these cells are activated, they hold the functionality of antigen presentation. Once this process occurs, mast cells then release TGF-β1 amongst other proteases to induce collagen fibrils and cellular effects due to fibroblast generation. In closing, these cells are also necessary for proliferation and differentiation of skin cells in conjunction with the tightening and relaxation of the ECM (Larouche et al., 2018).

b. Neutrophils

When identifying respondents during infectious conditions, neutrophils are first in line. As they are mainly identified by their DNA extracellular traps (NETs) which allow for engulfing of pathogens sensed during infection, these cells are crucial in wound healing models. As they travel from the blood to the localized inflammatory site rather quickly, it is clearly evident that these cells are at the forefront of protective wound healing. These cells also are able to generate the metabolic intermediates that produce an instant "oxidative burst". In neutrophils, the released chemokines are the result of activation of stratified keratinocytes. After this, there are blood platelets that garner the neutrophils to the area of injury. These specialized neutrophils can identify pathogens through the TLR-1, TLR-2 and TLR-10. They can be developed and activated through IL-17, IL-23, and the granulocyte-colony stimulating factor (G-CSF) which is the glycoprotein which simulates and releases granulocytes (in this case neutrophils) into the bloodstream. Cytokine IL-8, which is synonymous with the chemokine receptor 1 and 2 (CXCR1, CXCR2), plays the leading driving role of the chemotaxis. The key receptors in relation to the immunity of the skin and neutrophils are the chemokine ligand 12 and the chemokine receptor 4 (CXCL12), CXCR4). As these specialized granulocytes are able to use their enzymes to degrade pathogens within phagocytic cells, it is translated to the firm understanding that neutrophils are crucial mediators in wound healing (Wilgus, Roy, & McDaniel, 2013).

Studies have shown that patients with abberencies in their shuttling of granular neutrophils demonstrate greater risk for skin infections post-injury and complications during wound repair (Tsepkolenko, et al., 2019). Neutrophils are the main warehouses for matrix metalloproteinases (MMPs) by way of the granules and other vesicles of the cells. Specifically, MMP-2, MMP-8 and MMP-9 are the proteases whom's abilities were examined closely in wound healing. MMP-8 (aka collagenase-2) transcript mRNA levels are upregulated during wound sealing as a MMP-8 knockout mice showed a significant lag in wound closure, parallel with decreased levels of neutrophil extravasation. This is a clear indicator of MMP-8's progenitive role with neutrophil translocation in wound healing models (Tsepkolenko, et al., 2019).

c. Eosinophils

Eosinophils are decorated throughout the dermis and are key identifiers during allergy. The TLR receptors on these granulocytes are TLR-1, TLR-4, TLR-7, and TLR-10. The specialized cytolysis pathway has spearheaded the unloading of granules in eosinophils such as the major basic protein (MBP), the eosinophil cationic protein (ECP), and the peroxidase derived neurotoxin (EDN). These cells are able to fight against viral pathogens upon their activation of the granulocyte basophils and their daughter cells, mast cells. This double amplification generates a significant response in skin injury models. These eosinophils are fundamental in a caustic response during immune responses and stimulate the mediators involved in keratinocyte migration (Larouche et al., 2018).

d. Basophils

Basophils are effector cells that are specifically active in the innate immune system. Furthermore, the group of basophils which reveal TLRs-2, 3, and 4 provide these cells with their protective characteristics. These cells also have regulatory traits where they monitor the traffic of eosinophils by expressing the vascular cell adhesion molecule (VCAM-1) in endothelial cells. In reference to UV exposure in the skin, basophils have been shown to be active in combating inflammation as a large amount of these cells have been found in patient biopsies, thus elucidating the basophil's role in skin inflammation. (Voehringer D, 2017). They release histamines and cytokines IL-4, IL-14, and IL-3 to be involved in vascular permeability (Buckland, n.d.).

2. Natural Killer Cells

Although the design of these cells is morphologically absent of T and B cell markers, natural killer cells can still induce cytolysis, the process of cells bursting due to an osmotic imbalance within the cytoplasm. One of their main functions is to generate the cytokine family of interferons (IFN-γ) to assist in removal of tumor cells and clearing viral infections. The TLRs they express are TLRs 3,7, and 9. Other PRRs that belong to these cells are NOD2 and NLRP3 (Qui et al., 2010). During inflammation, these natural killer cells will localize to the skin using chemokine receptors that talk to the complimentary chemokine ligands in the keratinocytes.

3. Innate Lymphoid Cells (ILCs)

Innate lymphoid cells (ILCs) are a group of cells that have a colored resume of cytokines and transcription factors they can produce and express, relatively. Although these cells have different surface markers than B cells, DCs, T Cells, granulocytes and macrophages, they do have the cluster of differentiation markers 90, 25, and 127 (CD90, CD25, and CD127). These cells are part of a family of immune cells that are heterogeneous in their cytokine production profiles, transcription factor expression and effector functions. ILCs come from a familial lymphoid progenitor cells, and then future growth is dependent on CD132, the cytokine IL-7, the type-1 transmembrane proteins in concert of the Notch signaling pathway, and the DNA-binding protein inhibitor (ID2) gene (Björkström, Kekäläinen, & Mjösberg, 2013).

Innate lymphoid cells are then broken into categories of developing transcription factors paired with cytokine and cell lineage markers. Group 1 includes ILC's which produce IFN-γ from T-bet transcription factor. Group 2 ILCs are reliant on transcription factors GATA3-, RORα-, and TCF-1 and generate cytokines IL-5, IL-9, IL-13 and amphiregulin. Group 3 ILCs are dependent on RORγt and generate cytokines IL-17A, and IL-22. The ILC1, ILC2, and ILC3 groups are symmetrical to the adaptive cell groups Th1, Th2, and Th17 CD4+ T helper cell population. While ILCs do parallel the functionalities of CD4+ T cells, these phenotypically distinct cells are specific to respond in innate immunity alerts where there is no specific antigen necessary (Kim, Wojno, & Artis, 2013). ILCs can be found in the vast majority of tissues, they are saturated in the gut, skin and lung as active players in tissue homeostasis and inflammation. (Yang et al., 2017)

Table 1: A comprehensive makeup of the skin's innate and adaptive cells present in homeostasis and during injury. There are key identifiers of these cells and the cytokines/chemokines that they release as well as the localization of these cells. This table concludes the literature in this section into a clear conglomerate of the epidermal and dermal cells.

Skin Innate & Adaptive Immune Cell Populations					
Cell	**Cellular Family**	**Key Surface Markers**	**Cytokines/ Chemokines/ Granules (Proteins) Released**	**Skin Layer**	**Sentinel Role**
Keratinocytes	Skin Resident	TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR9, TLR10	NF-κB, IL-6, TNFα, CXCL20, CCL27	Epidermis	Pathogen Detection, Epidermal Composition
Merkel Cells	Skin Resident	CD200	CGRP, stromatin, VIP	Epidermis	Mechanoreceptor & Nociceptive Response
Melanocytes	Skin Resident	N/A	Melanin	Epidermis	Pigment Production & Trafficking
Dermal Fibroblasts	Skin Resident	TLRs 1-10	IL-6, IL-8, INFγ, TNFα, IL-12p70, IL-10, G-CSF, GM-CSF,	Dermis	Collagen, Elastin, & Structural Composition Initiates Inflammatory

			CCL1, CCL2, CCL5, CXCL1, CXCL8, CXCL10, CX3CL1		Signal Transduction
Endothelial & Epithelial cells	Skin Resident	E selectin, P selectin	TSLP, IL-33, and IL-25	Dermis	Antigen Presentation, Immune Regulation
Innate Immune Cells					
ILC	ILC	CD25, CD90, CD127	IFN-γ, IL-5, IL-9, IL-13, amphiregulin, L-17A, IL-22	Dermis, Epidermis	Tissue Homeostasis and Inflammation
Langerhan Cells	Skin Resident Cells	CD207, CD1a, CD11b, CD11c, MHC-II, F4/80, MMP-9, MMP-2, langerin+ Birbeck granules	N/A	Epidermis, Dermis	Antigen Presentation and Processing to Induce T Cell Response
Natural Killer Cells	Granulocytes	TLR3, TLR7,	IFN-γ	Dermis	Cytolysis, Viral

		TLR9, NOD2, NLRP3			Clearance
Neutrophils	ILC	TLR1, TLR2, TLR10	N/A	Dermis* *only during inflammation	Pathogen Engulfment via NETs
Basophils	Granulocytes	TLR2, TLR3, TLR4, VCAM-1	IL-3, IL-4, IL-13	Dermis	Granule Release
Eosinophils	Granulocytes	TLR-1, TLR-4, TLR-7, TLR-10	MBP, ECP, EDN	Dermis	Granule Release
Mast Cells	Granulocytes		TGF-β1	Dermis	Granule Release
Myeloid Dendritic Cells	Dendritic Cells	CD103+, CD141+, CD1C+, CD11b+	CCL22, CCL17	Dermis	Antigen Presentation, Phagocytosis
Plasmacytoid Dendritic Cells	Dendritic Cells	TLR7, TLR9	IL-6, IFN-α, IFN-β	Dermis	Antigen Presentation,
Monocytes/ Macrophage	Macrophage/ Phagocyte Progenitor	CCR-2, CX3CR-1, Ly6C+	TNF-alpha, IL-1, and IL-12.	Dermis	Wound Healing, Collagen

	Cell				Synthesis via Monocyte-Macrophage Axis
Resident Macrophages	Dendritic Cells	CD64, CD36, DC-SIGN, CD86,	IL-1β, IL-4, IL-6, IL-10, VEGF, TGFβ, TNFα,	Dermis	Wound Healing, Collagen Synthesis, Phagocytosis
Adaptive					
αβ T cell CD4+ T Cells CD8 + CCR4, CCR6, CCR8,CCR10	T lymphocytes		TH1: IFN-γ, IL-1, LT-alpha (IL-10 TH2: IL-4, IL-5, IL-13, IL-25, Amphiregulin, IL-10 TH17: IL-21, IL-17a, IL17f, IL-22 (IL-10) Treg: TGF-beta, IL-35, IL-10	Dermis	CD4 +: Generate TH1, TH2, TH17, Treg CD8+: with virus and immunity against virus and neoplastic cells
Natural Killer T Cells	Innate Immune Cells			Dermis	
γδ T cell	T lymphocytes	TLR-1, TLR-3,	IFN-γ	Dermis	Predominantly to the dermis

		NLR-1, NLR-4			of mice cells.
B- Cell	B- Cells		IgG, IgA, IgM, IgE), GM-CSF	Dermis	Chronic inflammaotry skin (AD, cutaneous leishmaniasis)

F. Adaptive Immune Cell Demographics

1. Epidermis

While the Langerhan cells reign as one of the top contenders throughout the epidermis, the skin-resident memory T cells are first in line during adaptive immune responses to secondary antigens, serving as key effector cells. The skin houses two times as many T cells than in the blood in addition to having 98% of cutaneous lymphocyte-associated antigens stationed in the skin during physiological circumstances (Boyman et al., 2006). In psoriatic skin, lesions develop quicker than healthy, normal skin in murine models without type I and type II IFN receptors (Boyman et al., 2004). With this presented deficiency in immune regulatory proteins, the necessity of skin-resident memory T cells is worthy of investigation. Following the aforementioned study, researchers looked into the kinetic activity of T cell expansion in psoriatic skin, discovering a significant increase in dermal T cells prior to the progression of psoriatic transformations in the epidermis (Conrad et al., 2007). As these changes occur once T cells cross into the epidermal basal layer, the conclusive discovery of T cell activation and their expansion is a precursor to the pathology of the epithelium stands supported. Additionally, the dynamic relationship between basal T cells and keratinocytes is fundamental for this epidermal pathophysiology. The very late antigen 1 (VLA1/ α1β1 integrin) expressed on basal membrane T cells and it's interaction with collagen IV, provides a key pathway for migration of the skin-resident T cells (Wakim et al, 2008). In addition to VLA1, skin-resident memory T cells have also been shown to express CD103 for skin homeostasis and protection against harmful pathogens (Gebhardt et al, 2009).

Human Simplex Virus infections also show the relevance of skin-resident memory T cells in immune response. A mouse model showed that the skin-resident memory T cells and CD4+ T cells provide the proliferation of memory CD8+ T cells (Wakim et al., 2008). Studies outside of human skin models show that there are three specific phases of immune responses involving T-Cells. The first is mainly of tissue-resident memory T cells, the second is the gathering of non-specific circulatory memory T cells and the third involves antigen-specific T cells that drain to the lymph nodes (Woodland & Kohlmeier, 2009). This provides a clear understanding about the importance of skin-resident memory T- Cells in the immunogenesis of skin conditions.

αβ T lymphocytes

As aforementioned, these are cells that congregate at the epidermis through circulation in the blood and chemokines secreted by local keratinocytes. The affinity of these T cells to the epidermal tissue is a result of the cutaneous lymphocyte antigen (CLA+) T cells via the vascular lectin endothelial cell-leukocyte adhesion molecule (Berg et al., 1991).

2. Dermis

a. CD4 + T Cells

TH1, TH2, and TH17 cells are the main types of CD4 + Tcells found in the skin during inflammatory skin disease. In times of infection of the skin, Th1 cells that produce IFNγ can activate macrophages and kill pathogenic organisms in between cells. In normal conditions, Th1 cells are associated with autoimmunity and pathologies related to immune-driven conditions as in psoriasis. TH2 cells moreso are connected to allergic disease such as eczema (atopic dermatitis) and allergen-stricken diseases, whereas TH17 cells have recently been tied to roles in psoriasis (Di Cesare, Di Meglio, & Nestle, 2009) and atopic dermatitis while being at the frontline against a multitude of fungal and bacterial infections (Weaver et al., 2007). To further indulge in TH17's potential responsibility for skin disease such as chronic mucocutaneous candidias is due to a perturbed IL-17 (the cytokine released by TH17) mediated immune response based on genetic defects which unveils autosomal-dominant hyper-IgE syndrome as well as autosomal-recessive vulnerability to mycobacterial disease (Eyerich et al., 2008). These diseases related to the CD4+ T cells are identified by the frequent and repetitive mucosal and skin membrane infections. As mentioned previously, a presumed mechanism for the battle

against pathogens with IL-17 and IL-22 responses in the skin is due to the upregulation of AMP production via epidermal keratinocytes. As these are cytokines released by TH17 cells, these subset of T helper cells connect immune and epithelial cells to optimize the host's immune response against foreign dermal pathogens. There has been a subset of T cells that specfically secrete IL-22 cells, titled TH22, recently unveiled. In the presence of IL-6 and the TNF family, plasmacytoid dendritic cells are effective in generating these TH22 cells. Similar to Th17, these cells have also been seen in skin of patients with atopic dermatis; understanding their future role in skin pathogenesis and homeostasis is ideal for the future of dermatological science (Nograles et al., 2009).

b. γ Delta T Cells

Another cell type in the dermis includes the γδ T cell subset which are identified by the γ and δ T Cell receptor (TCR) chains. They are thymic progenitor cells that have grown and survived elsewhere in the periphery and consitute for up to 5% of these peripheral, CD3+ cells post-synthesis of embryogenesis (Bonneville et al., 2010). As these γδ T cells are barrier-tissue resident cells that are present in both human and mice cell lines, the morphology of mice γδ T cells takes on a more dendritic form while human cells are more peripheral blood cells. γδ T cells localize based on the chemokine receptors expressed by way of released cytokines via epidermal keratinocytes (Havran, Chien, & Allison, 1991). The majority (over 80%) of these cells do express the CCR5 that shuttles the migratory transport of γδ T cells to the localized inflammatory area. γδ T cells have a small inventory of recognizing antigens. Their capabilities include not needing main histocompatibility complexes (MHCs) and costimulating molecules (CD28, CD30 etc.) to respond and recognize antigens due to TLR-1 and TLR-3 that recognize PAMPs (Havran, Chien, & Allison, 1991). The inflammation created causes an increased expression of the NOD-like receptor-4 (NLR-4). γδ T cells are able to improve the anti-infectious resistance through mainly generating IL-17 aftter they migrate to the dermal area post-infection of bacterial pathogens or injury. The decreased activity of delayed-type hypersensitivty effector cells, alongside the generation of IFNγ, activating dendritic cells, and aiding in maturation and cytokine productions (Cruz et al., 2018). These γδ T cells identify stress proteins in the presence of the transmembrane proteins, NKG2D and NKG2. Immediately after this, these γδ T cells, synthesize chemokines, cytokines, effectors(IFN-γ), and keratin growth factors (KGFs) locally thus inducing cell lysis (Cruz et al., 2018). γδ lymphocytes are the first responders to skin trauma

and can rapidly alter their morphology. The activation tissue marker, CD69, is expressed and thus produces chemokines that recruit inflammatory cells to the cellular matrix (Marshall et al., 2019). These actions are able to regulate inflammation, cellular cytotoxicity and wound healing. Furthermore, these cells can interact with keratinocytes, helping their survival and function, to aid in rebuilding the epidermis upon direct damage.

c. Natural Kill T Cells (NKT)

Natural Killer T Cells (NKT) are apart of the innate immune system, although they are thymic cells. These NKT cells are different cells in that they only have an invariant V alpha-14 and Vbeta-11 rearrangement receptor in humans (Godfrey et al., 2004). This Valpha-24 and Vbeta-11 rearrangement receptor provides NKT cells to identify antigens specific to glycolipids by way of the antigen-presenting molecule CD1d on MHC I (Sieling, 2000). Most molecules associated with these lymphocytes are located in the periphery. As for the lymphatic cells in the bloods, the NKT cells are roughly 1% of the entire population, and are at a significantly lower rate in the dermis. They are the main sources of the IFNγ and other cytokines in regards to pathogenic defense. Outside of IFN-γ, IL-4 also participates in the antigen-specific, CD8+ T-cell and dendritic cell function in resident tissue (Sielling, 2000).

d. B-Lymphocytes in the Dermis

B Cells from the humoral stem of the immune system are the primary source of specific antibody producution. These cells also can operate outside of antibodies and acts as APCs to then generatie cytokines both locally and systemically. There are a vast variety of emerging studies that reflect B cells having a significant role in dermatoses and homeostatitc skin conditions. The proinflammatory and immune regulation of Bcells have also deemed them essential amongst the tumor microenvironment of melanoma afflicted skin. As we garnish more information from mammaliam skin models, the idea that B lymphocytes are apart of the dermal immune system gains further confirmation (Egbuniwe, Karagiannis, Nestle, & Lacy, 2015)

In the skin, the CLA guides T cells to the skin. The antigen binds to the surface adhering protein E-selectin that is upregulated under vasodialation in inflammatory conditions in the skin. However this protein is rather low in levels of normal, non-inflamed skin. The CLA protein is expressed in circulatory, memory B cells that are also upregulated in vitro. This method of

upregulation enhances CLA binding to e-selectin and supports the notion that proper stimulatory conditions will induce the CLA binding process in B lymphocytes as a means for cutaneous migration. However, other e-selectin ligands are expressed on B cells as there are different isofroms of glycoproteins that the CLA antigen falls under. In regards to the skin, less is known about the receptor-ligand couples that do control the B cell homing in cutaneous microvenvironments (Egbuniwe, Karagiannis, Nestle, & Lacy, 2015).

In normal skin of mice and humans, skin-associated B Cells do recirculate or are skin-resident. They localize to the deep dermis whre they then are spread out individually in homeostatic conditions as either clusters or lymphoid structures. These heterogenous cells include conventional B-2 cells and B-1 cells. There is a suggested subset of B cells that resemble the conventional B-2 cells which express high levels of IgM and cell surface markers such CD11b. These B cells identify pathogens and generate organic Abs sans T-Cells at the beginning of infection, mostly IgM and IgA and in murine models, the cytokine GM-CSF. In regards to human skin models, secretion of IgA is found in eccrine sweat glands, sebum and sweat. The antibody secretion of IgG and IgM is found at the skin surface, although this route is unknown. Interetingly enough, IgG in sweat found on the skin surface can bind commensal bacteria S. aurues. As the origin of these Abs are to combat and regulate skin pathogens, they can be detrimental to dermal autoantigens in an automated antibody process (Debes & Mcgettigan, 2019).

B lymphocytes are genrally considered to be systemic, thus contritbuting to autoimmune and inflammatory skin diseases. The nubmers are upregulated in dermatoses such as psoriasis, scleroderma, atopic dermatitis, allergic contact dermitis and more. Further studies need to be conducted to identify whether or not B cells contribute to inflammation of the skin through localized effector fuctions as these cells are infiltrating the tissue in a number of dermatose pathologies. Upon their activation, B lymphocytes are known to be effector cells in inflammation as they secrete a number of inflammatory cytokines such as GM-CSF, IL-6, IFN-γ, and IL-4. Recent studies have shown that during skin fibrosis and thickening, skin pathology had been reduced in B cells that lacked expression of IL-6, showing pathogenic roles for this cytokine-lymphocyte axis. Furthermore another subset of B Cells are regulatory B cells that involve exrpression cytokines Il-35 and Il-10, maintainence and widespread production of regulatory T cells, and adenosine generation. In wound healing models, scientists propose TLR-4 induces

upregulation in IL-6, IL-10, TGF-beta, PDGF, and FGF for the source of B-Cell generated wound healing. As this is a relatively new field in dermatoimmunology, more studies can look into the subsets of B-cells and their role in wound healing therapeutics (Debes & Mcgettigan, 2019).

G. Most Common Dermatoses

Eczema, psoriasis, acne vulgaris, pruritus, alopecia areata, decubitus ulcer, urticaria (hives), scabies, fungal skin diseases, impetigo, cellulitis, viral warts, molluscum contagiosum, non-melanoma skin cancer, abscess and other bacterial skin diseases are the 15 most common dermatoses of the world (Johns et al, 2013). Uncovering the impact of these specific skin diseases provides direct suggestions as to what doctors should be leaning towards when it comes to public health matters. Through following the cascade of burden globally, dermatological scientists and skin biologists must converge their thinking into strategic management and control of skin disease which efficiently and necessarily utilise health resources in addition to withholding the rank of dermatoses in comparison with other diseases.

IV. Statement of Purpose

The purpose of this review is to understand the epidemiology and pathophysiology of common skin diseases affecting the people of West Africa. Primary contributors to these common diseases found not only globally, but additionally funneling through, Africa and West Africa were identified in order to make recommendations for improvement of dermal healthcare regulations.

While other research has focused on identifying the epidemiology of skin disease in these regions through direct patient surveying and clinical observation by medical professionals and self-referrals, this research will specifically focus on updating and quantifying these epidemiological factors that may give rise to the full scope of these the region rather than specific countries. As a result of this research, specific recommendations to lessen the burden of skin disease, particularly in the Economic Community of West African States (ECOWAS) conglomerate, is proposed.

V. Methods of Literature Review

Skin disease is categorized through the International Classification of Diseases, Ninth Revision (ICD-9), as well as diseases of the hair, nails, eyelids, external genitalia and ear. In addition any damage done to the skin from outside causes are grouped into this ICD-9 category. From this definition, according to the Journal of American Academy of Dermatology, there are 24 categories that group these diseases into one space.

Each article analysed in this analysis was taken from a 20-year span of January 2000 to December 2019. The selection of articles was fine-tuned by identifying the distribution of skin disease, revealing the populations affected (age, gender, ethnicity, etc), the main causes, country of origin, the prognosis of disease, and the pathology of the specific skin condition. Studies were included that were conducted from observational inpatient/outpatient clinics in West Africa without exclusion of any group. Each article reviewed includes observational studies by general practitioners, internists, dermatologists, and/or nurse practitioners in the area. When identifying the immunopathologic pathways, there are genomic markers and factors that contribute to the phenotypic expression of these immune responses. To understand the pathology of each skin disorder, peer-reviewed scholarly journal articles were used for the general guidance of the prognosis as well as for the explanation of the pathogenesis and pathophysiology of each disease.

Studies were exclueded that found skin disease as sequale of larger disease studies (HIV, AIDs, diabetes etc). The focus of the review was to include solely West African disease including studies related to scabies, studies that included solely one demographic (i.e children), as well as studies that included specific regions of varying areas (rural and urban areas). Studies that covered all types of skin disease were included in order to get an full visual of any skin disease found in West Africa. Articles that are literature reviews of direct observational studies served as a reference for framework of this paper, but their direct findings were not included in statistical skin disease analysis, although they may have similar findings.

24 research articles that spanned over four West African countries: Benin, Cameroon, Ghana and Nigeria. Each article contributed a portion of the total patient count that relates to the total frequency of disease frequency. Benin studies contributed a total of 246 patients, Cameroon contributed 248, Ghana contributed 3,900 and Nigeria contributed 31,762 patients to the study. The total amount of patients surveyed was 34,709. The relative frequency is calculated by the (frequency of disease)/ (total frequency of disease). Each of these studies reported their

prevalence rates through tables. After the diseases were compiled in one tables, the dermatoses were then sorted by relative frequencies from the largest to smallest of the top 15 Dermatoses.

There are over 400 diseases that were organized into 24 categories through Fitzapatrick's Dermatology, a standard guideline in dermatology. The top 15 dermatoses went through a 2-sample z test for equality of proportions for West Africa vs the United States. One study was used to identify the relative frequency of dermatoses in the United States (Lim et al., 2016), the United Kingdom (Doe et al., 2001), and Jamaica (Dunwell & Rose, 2003). The total amount of patients that was calculated for the rest of the world was 84,529,077. The count data from the United States was calculated from the study by taking the relative frequency and multiplying it by the population of the United States. From results of the statistical analysis provided the list of the 7 statistically signifcicant diseases that are reviewed in this paper. The top 15 dermatoses aforementioned also were placed into 9 categories and the same 2-sample z test for equality of proportions for West Africa vs the United States was conducted. Signficant diseases are indicated with asterisks*. The top 15 categories belong to categories that include dermatoses outside of the sole dematitis itself. This allowed up to see where the categories of the top 15 dermatoses ranked in overall rate of incidence in West Africa.

A. Distribution of Skin Disease

In regard to the distribution of the skin disease, the rate of incidence and prevalence was reviewed. This lightly touches the epidemiological factors that influence the rates of incidence, patient profile, and predisposed populations.

B. Etiology of Disease

The etiology of the diseases was included by understanding the original pathogen taxa for the skin condition.

C. Pathology

The pathology and histology of the diseases are reviewed through primary and secondary sources to show the microscopic view of tissue in a diseased state. For consistency of data, and ease of analysis, the pathology of the skin disease will discuss the cells active and the afflicted

location in the derms and epidermis. The prognosis of disease will be closely reviewed by the conducting institution.

D. Metrics of Classification of Skin Disease Severity

When generally reviewing the burden of skin disease, the metrics are most important. One specific group of metrics are the years of life lived with disability (YLD) and years of life lost (YLL) (Aksut, Dellavalle & Naghavi, 2017). Together these two criteria place each skin disease in a tier system. Uncovering a solution to skin disease that affects large populations with low YLL versus a solution regarding skin disease involving a smaller number of individuals with a high YLL is the resounding question at the end of this global debate.

Keywords that are used in the electronic database search are noted and will include the terms: West Africa, global, skin, disease, dermatoses, epidemiology, pathophysiology, Africa, disorder, dermatologic, prevalence, hospital, clinic, cutaneous, conditions, incidence, pattern, Nigeria, Ghana, Benin, Cameroon.

The results of this literature review are visually organized using tables that include the disease, population (age, gender, ethnicity) most affected, distribution of occurrence (which relates to the specific percentage of people that are receiving this disease in proportion to the general population, displayed as a percentage), main epidemiological cause of dermatosis, prognosis, pathology, and references.

1. Graphs include Venn diagrams that compares and contrasts the dermatoses between West African and the United States, histology and pathology of the statistically significant dermatoses, and sample images of the phenotypic manifestation of each skin disease.
2. The immunopathogenesis in relation to the cytokine profile of the most abundant dermatoses are given.
3. Statistical analysis of the quantity of skin diseases was performed using a meta-analysis method of 24 peer-reviewed articles that include the skin diseases aforementioned. For occurence of dermatoses in West Africa, the frequency of each skin condition was calculated by ICD-9-Dermatological Category and for the cumulative frequency of the entire peer-reviewed study. Dermatoses that are categorized under ‘Other’ are excluded as their true identity is not revealed to make a significant conclusion on the disease. The

data was wrangled from percentages of each study to create count numbers for each skin disease. The relative frequency was multiplied by total number of participants for each study, to get the total count for that exact dermatosis participant count. After this, the dermatoses were sorted through RStudio software by their total counts of patient disease. Group totals and individual dermatosis totals were sorted.

i. After a collection of the top dermatoses through sorting, statistical analysis of each of these diseases compared to the US rate of incidence was analyzed using a two proportions z test to compare West African Disease counts to the US disease counts. Acne Vulgaris in West Africa was categorized as Acne (unspecified) in the United States. Localized Vitiligo and Vitiligo in the United States was grouped into one category for our statistical analysis. Any diseases without counts was considered NULL for R statistical analysis, as this number was not observed. P-values of ≤ 0.05 are considered statistically significant.

VI. Results of Literature Review

The top dermatoses responsible for disability-adjusted life years (DALY) and years lived with disability (YLD) worldwide are the following dermatoses: dermatitis,, acne vulgaris, urticaria, psoriasis, viral skin diseases, fungal skin diseases, scabies, melanoma, pyoderma, cellulitis, keratinocyte carcinoma, decubitis ulcer, alopecia areata, pruritis, with the remaining dermatoses falling under the miscellaneous 'Other skin and subcutaneous diseases' category (Karimkhani et al., 2017)

A. Common African Skin Diseases

The top 15 common skin diseases of West-Africa ranked by count and relative frequency are Atopic Dermatitis (RF: 7.49%), Pityriasis (Tinea) Versicolor (RF: 4.94%), Acne Vulgaris (RF: 3.73%), Papular Urticaria (RF: 3.47%), Tinea (unspecified dermatophytosis) (RF: 2.94%), Contact Dermatitis (RF: 2.94%), Scabies (RF: 2.76%), Seborhheic Dermatitis (RF: 2.50%), Pityriasis Rosea (RF: 2.26%), Urticaria (2.18%), Human Pappilomavirus / Viral Warts (1.85%), Tinea Capitis (RF: 1.80%), Lichen Planus (1.77%), Vitiligo (RF: 1.77%) and Lichen Simplex Chronicus (RF: 1.45%).

Based on the results of a 2-sample test for equality of proportions with continuity correction, there is a statistically significant difference between atopic dermatitis ($p < 2.2e-16$), acne vulgaris ($p < 2.2e-16$), urticaria ($p < 2.2e-16$), contact dermatitis ($p<2.2e-16$), sebhorreic dermatitis ($p < 2.2e-16$), human pappilomavirus ($p = 1.708e-6$) and vitiligo ($p < 2.2e-16$) in West African individuals vs individuals in the United States. Atopic dermatitis has a higher relative proportion in West Africa vs the United States (.0749 and 0.0099, respectively). Acne vulgaris has a higher relative proportion in West Africa vs the United States (0.0373 and 0.0163, respectively). Urticaria has a higher relative proportion in West Africa vs the United States (0.0218 and 0.0072, respectively). Contact dermatitis has a higher relative proportion in West Africa vs the United States (0.0294 and 0.0417, respectively). Sebhorreic dermatitis has a higher relative proportion in West Africa vs the United States (0.0250 and 0.0135 respectively). Human pappilomavirus has a higher relative proportion in West Africa vs the United States (0.0185 and 0.0153, respectively). Vitiligo has a higher relative proportion in West Africa vs the United States (0.0177 and 0.0057, respectively)

The top categorical dermatoses in of West-Africa ranked by count and relative frequency are summarized in Table -----. These are Dermatitis (RF: 22.09%), Fungal Diseases (RF: 16.53%), Infestation, Bites, and Stings (RF: 7.84%), Viral Diseases (RF: 6.04%), Acneiform (6.03%), Lichenoid and Granulamatous Disorders (RF: 4.49%), Melanocytic Disorders (RF: 4.08%), Psoriasiform Disorder (RF: 3.90%), Neutrophilic, Eosinophilic, and Mast Cell Disorders (RF: 3.20%). To reiterate, these relative frequency numbers are based on the frequency of the disease divided by the total frequency of the patient disease count.

Based on a 2-sample test for equality of proportions with continuity correction, there is a statistically significant difference between categorical classifications of Dermatitis ($p < 2.2e-16$), Psoriasiform Disorder ($p < 2.2e-16$), Viral Diseases ($p < 2.2e-16$), Lichenoid and Granulamatous Disorders ($p<2.2e-16$), Melanocytic Disorders ($p < 2.2e-16$), Neutrophilic, Eosinophilic, and Mast Cell Disorders ($p = 1.708e-6$) and Acneiform ($p < 2.2e-16$) in West African individuals vs individuals in the United States.

1. Dermatitis

Under the inflammatory category of the top 15 ECOWAS dermatoses are the eczemas, atopic dermatitis, contact dermatitis, lichen simplex chronicus, and seborrheic dermatitis..

2. Psoriasiform Disorders

Psoriasiform disorders include pityriasis rosea as the dermatosis in this category of the top ECOWAS dermatoses.

3. Infestation, Bites, and Stings

Papular urticaria and scabies are the dermatoses in this category of the top ECOWAS dermatoses..

4. Fungal Disorders

Diseases under the infectious fungal classification include tinea capitis and tinea (unspecified), pityriasis (tinea) versicolor in this category of the top ECOWAS dermatoses..

5. Viral Diseases

Human papillomavirus (viral warts) as the dermatosis in this category of the top ECOWAS dermatoses..

6. Licheoid and Granulamatous Disorders

Lichen planus is the dermatosis in this category of the top ECOWAS dermatoses..

7. Melanocytic Disorders

Melanocytic disorders also include pigmentary disorders such as vitiligo as the dermatosis in this category of the top ECOWAS dermatoses..

8. Neutrophilic, Eosinophilic, and Mast Cell Disorders

Urticaria is the dermatosis in this category of the top ECOWAS dermatoses.

9. Acneiform Disorders

Acneiform Disorders include acne vulgaris as the dermatosis in this category of the top ECOWAS dermatoses.

Table 2: This table demonstrates the rates of prevalence of the top 15 dermatoses in both West Africa and the United States.

Disease	# of West African Occurrence	# of United States
Atopic Dermatitis*	2601	836790
Pityriasis (Tinea) Versicolor)	1716	NULL
Acne Vulgaris *	1296	1377744
Papular Urticaria	1205	NULL
Tinea (Unspecified)	1089	NULL
Contact Dermatitis *	1021	3524659
Scabies	957	NULL
Sebhorreic Dermatitis *	866	1141077
Urticaria*	756	608574
Pityriasis Rosea	786	NULL
Human Pappillomavirus *	641	1293220
Tinea Capitis	624	NULL
Lichen Planus	616	NULL
Vitiligo *	616	482071
Lichen Simplex Chronicus	504	NULL

Table 3: The relative frequencies of the ECOWAS dermatoses and the their US RF counterparts. The statistically significant dermatoses are indicated with an asterisk (*).

Disease	Relative Frequency ECOWAS	Relative Frequency US
Atopic Dermatitis*	7.49%	0.99%
Pityriasis (Tinea) Versicolor)	4.94%	0.00%
Acne Vulgaris *	3.73%	1.63%
Papular Urticaria	3.47%	0.00%
Tinea (Unspecified)	2.94%	0.00%
Contact Dermatitis *	2.94%	4.17%
Scabies	2.76%	0.00%
Sebhorreic Dermatitis *	2.50%	1.35%
Urticaria	2.18%	0.72%
Pityriasis Rosea	2.26%	0.00%
Human Pappillomavirus *	1.85%	1.53%
Tinea Capitis	1.80%	0.00%
Lichen Planus	1.77%	0.00%
Vitiligo *	1.77%	0.57%
Lichen Simplex Chronicus	1.45%	0.00%

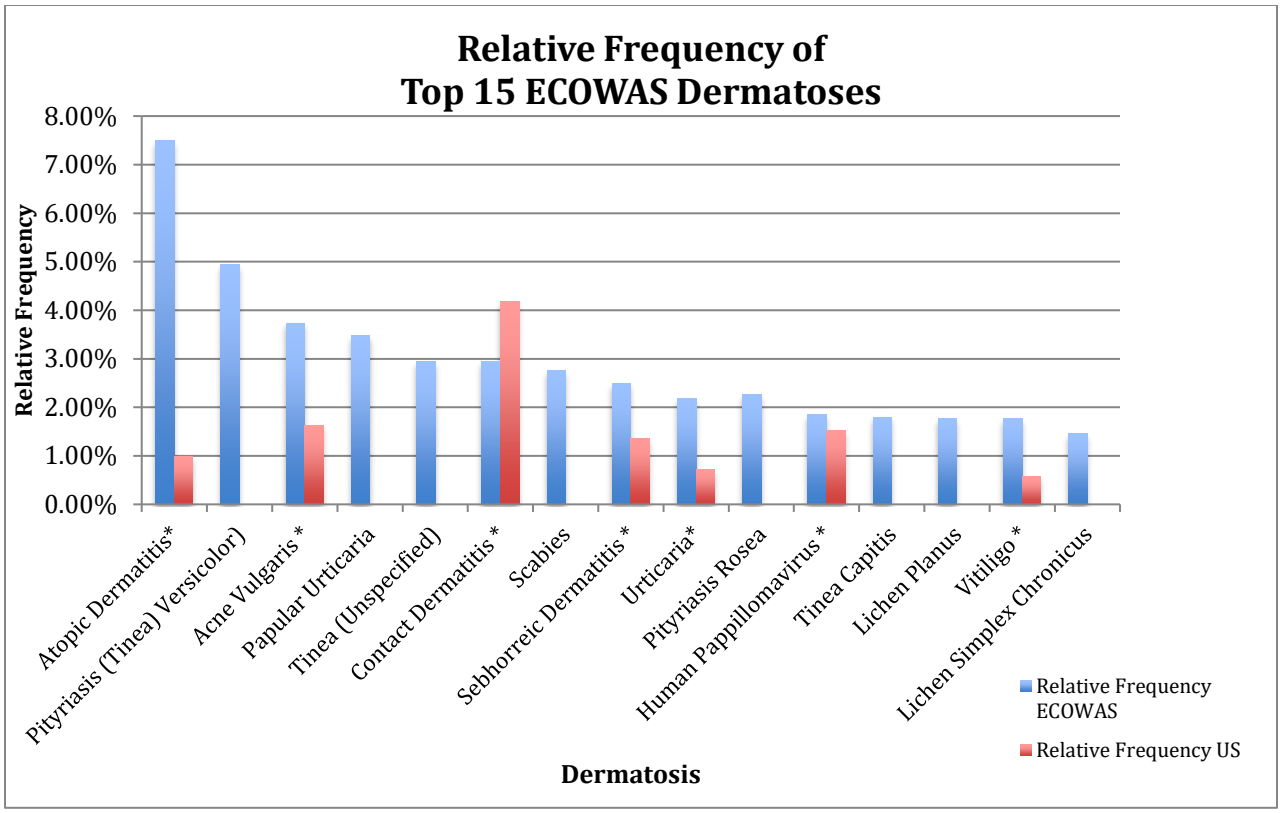


Figure C: The performed 2-sample z test comparing the relative frequencies (RF)of the top 15 dermatoses in ECOWAS in comparison to the RF in the United States. Statisticaly significant diseases in comparison to the United States RF are indicated with *.

Table 4: The dermatoses categorical classification based on Fitzpatrick Dermatology (Kang et al., 2019) disease categorization. The second column accounts for the number of dermatoses from the top 15 ECOWAS diseases that belong in the corresponding categories. These categrories are the only groups selected for statistical analyisis against their corresponding groups in the US. The average categorical disease frequency is calculated in the third column and the corresponding categorical diseases for the US are in the 4th column.

Disease Category	Top 15 Categorical Group Total	Overall ECOWAS Count	Avg Categorical Disease Frequency ECOWAS	Avg Categorical Disease Frequency US
Dermatitis	4	7768	22.09%	6.51%
Psoriasiform Disorder	1	1355	3.90%	0.51%
Infestation, Bites, and Stings	2	2722	7.84%	0.00%
Fungal Diseases	3	5737	16.53%	0.00%
Viral Diseases	1	2095	6.04%	7.28%
Lichenoid and Granulamatous Disorders	1	1558	4.49%	0.96%
Melanocytic Disorders	1	1415	4.08%	0.57%
Neutrophilic, Eosinophilic, and Mast Cell Disorders	1	1111	3.20%	0.72%
Acneiform Disorders	1	2093	6.03%	1.63%

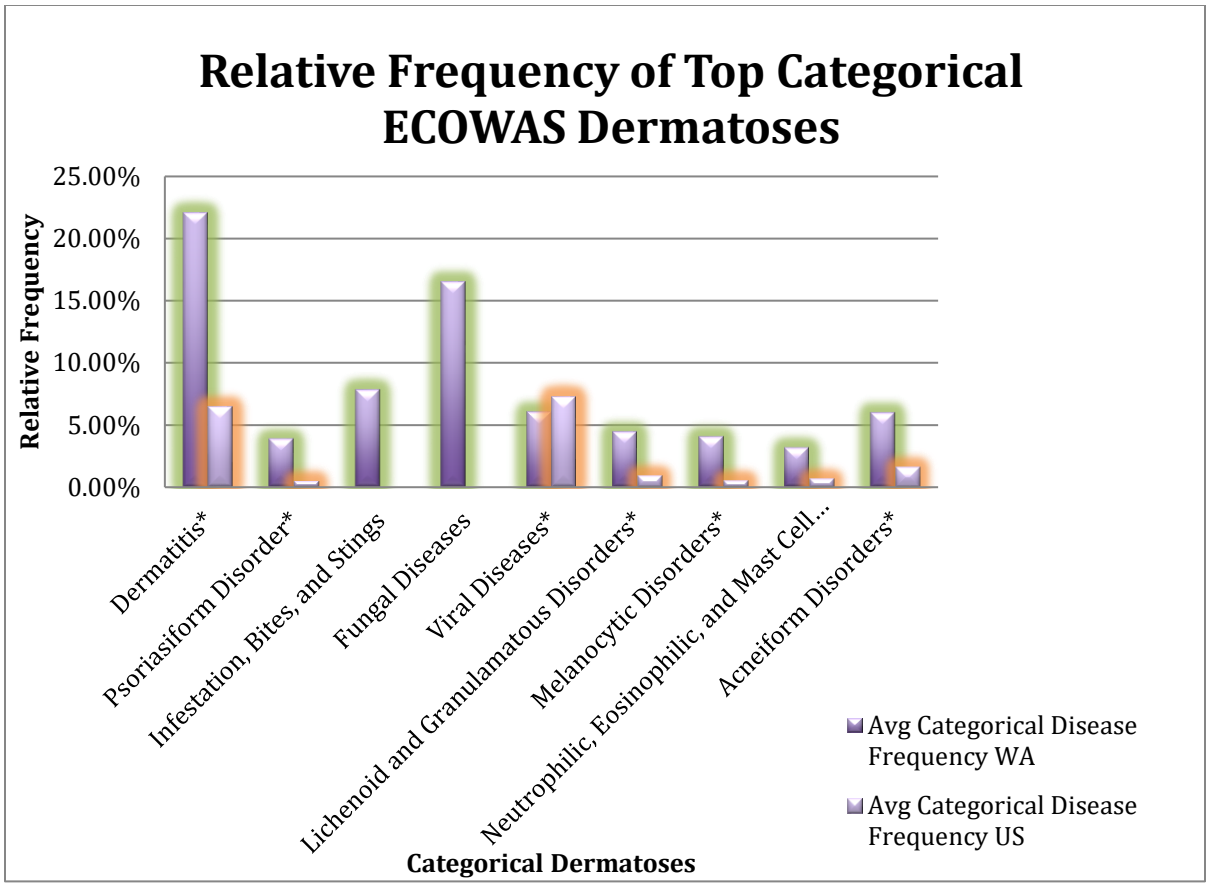


Figure D: The performed 2-sample test comparing the relative frequencies (RF) of the categorical top 15 dermatoses in WA in comparison to the relative United States. Statisticaly significant diseases in comparison to the United States RF are indicated with (*).

B. Common West African Skin Diseases

1. Atopic Dermatitis (Acute, Subacute, Chronic)

Incidence & Prevalence (Frequency):

The inflammatory disesase atopic dermatitis is diagnosed through the pruritic rashes that plague the patient's skin. Of those mostly affected by this condition, children unfortunately commonly fall ill to this disease. The age of onset is roughly one to twelve years old. It is at this age where over 60% of the affected patients will have their atopic dermatitis resolve itself (Odhiambo, 2009). Although common to the general public, this form of dermatitis occurs frequently in those genetically predisposed and animal caregivers (Katsarou & Armenaka, 2011). Lifestyle plays a significant role in the acquisition and exacerbation of this disease. Lifestyles of taking hard, hot showers can accelerate the production of scales on the face, cheek, ands legs for adults (infants and children included). With having at least one parent suffering from atopic

dermatitis, there comes a 50% possibility or more of an offspring having the condition as well (Barnes, 2010).

Etiology

The etiology of atopic dermatitis is uknown however there are genetic and environmental components to it. One bacterial organism responsible for example, is the bacteria staphyloccoccus aureus. The S.aureus species is a commensal and pathogenic bacteria is apart of an indoviduals skin microbiome, or skinome. A collective study showed that infants aged as young as three months, afflicted with atopic dermatitis, show a significant increase in S. aureus as compared to their non-affected age-mate counterparts (Meylan et al., 2017).

Risk Factor (race, sex, age)

As aforementioned, roughly 60% of atopic dermatitis cases onset at the age of a few months to 12 years old. If one parent has atopic dermatits, the poassibility of the child bearing the disease is well over 50%. Hot, hard showers give rise to the puriritic scales on the skin in addition to the socioeconomic and lifestyle factors such as tress, smoking, exposure to dander from animals, which give rise to the hygeine hypothesis (Tay et al., 2002).

Pathogenesis

Cells Involved

From an immunological standpoint, atopic dermatitis is a TH2-acute immune response regulated by the cytokines IL-17, IL-23. This then gives the downstream release of cytokines IL4, IL-5, IL-13, which downregulate AMP production, thus creating an overactive immune response, which phenotypically manifests as upregulated inflammation and itching (Howell et al., 2008). On the other hand, chronic atopic dermatitis, is driven through a TH1-actute immune response with release of cytokines IL-12 and IFN-γ (Yamanaka & Mizutani, 2011). During the atopic dermatitis response, the filament-aggregating protein, fillagrin, is broken down and loses function with transepidermal water loss. This dermatitis is deficient in ceramides (and sphingolipids) together in the stratum corneum which leads to poor skin barrier (Danso et al., 2014). This then exacerbates the condition and leads to more inflammation and itching.

Cytokines

IL-4 is a regulatory cytokine in this condition that activates the TH2 cells which then release IL-5 to activate eosinophils, IL-13 and upregulation of IgE production. These cytokines generated help downregulate TLR levels thus lowering AMPs and reducing the amount of lipids in the stratum corneum (Noda, Krueger, & Guttman-Yassky, 2015). This gives reason as to why you will see atopic dermatitis with fewer antimicrobial peptides while psoriasis has little to no staphyloccocus bacteria with upregulation of AMPs (Howell et al., 2008).

During atopic dermatitis, the immunological factors also affect the skin microbial compositions. AMPs have an important role in preventing pathogenic microbes from infecting the skin (Kwiecien et al., 2019). The two main classes of AMPS in the skin are cathelicidin and beta-defensins (DEFBs) which are able to destory S.aureus in vitro. When you compare levels of cathelicidin and DEFB-2 and 3 in psoriasis, there is a significant decrease in these AMPs when compared with psoriatic skin. The other IL-10 cytokine from TH2 cells are also shown to have decreased expression in AMPs (Kim et al., 2016). More recently, cytokines IL-17, IL-18, IL-31 have been recently discovered to be upregulated in atopic dermatitis lesional skin (Kim et al., 2016).

S. aureus in AD disease

In relation to AMPs, the overgrowth of S.aureus will be synonymous with a decrease of AMPs in atopic dermatitis lesions. The correlation between TLR-2 and cathelicidin AMP reflects an increase in both levels of proteins (Schmid, Andreas et al., 2017). There are virulence factors secreted by S.aureus which is the superantigen factor. This superantigen that α-toxin is known to increase the severity of atopic dermatitis through inducing cell lysis and being toxic to keratinocytes while also stimulating IgE responses. Upregulated levels of TH2 cytokines lower the fillaggrin expression and sphingomyelinase, inducing the continuous cycle of keratinocyte susceptibility to that α-toxin. This results in the poor barrier function and permeation of irritants and various allergens in atopic dermatitis (Dou et al., 2019).

This results in excessive production of T cell cytokines which causes cytotoxicity. SAgs are also allergens and stimulate an Immunoglobulin-E (IgE) response. Another factor is α-toxin that has been proposed to increase AD severity. The α-toxin monomers form a heterodimer complex on the cell membrane that creates a porous channel leading to cell lysis. It has been

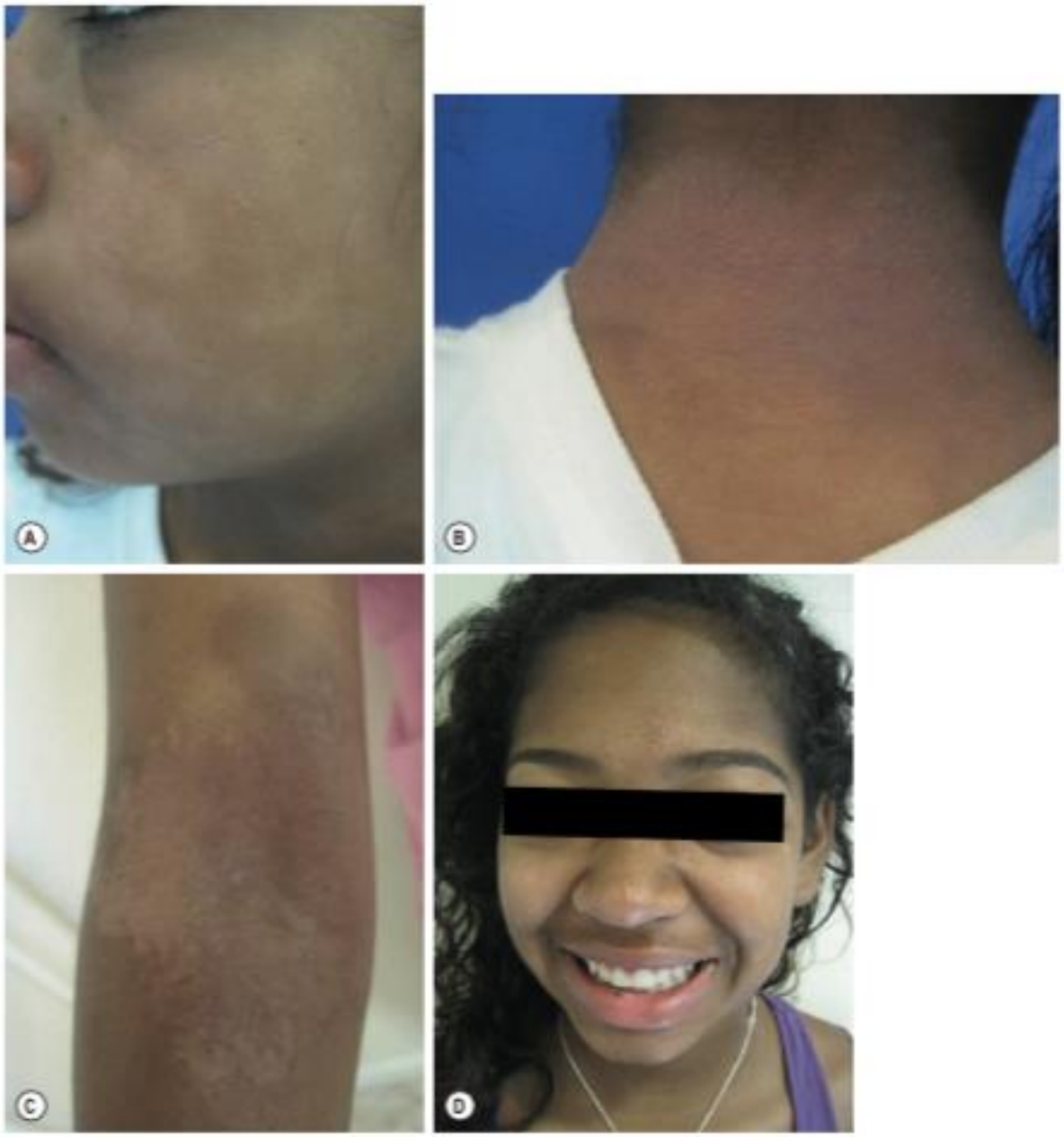
shown that α-toxin is severely toxic to keratinocytes. In AD, high levels of Th2 cytokines reduce expressions of filaggrin and sphingomyelinase, making keratinocytes more susceptible to α-toxin. This can result in loss of barrier function, increase in penetration of irritants and allergens and development of AD (Dou et al., 2019).

Gut Microbiome in AD

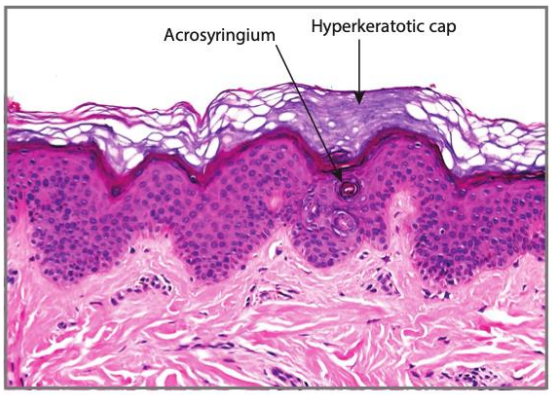
Through the use of probiotics, the gut mirobiome can regulate the immunologic pathway in atopic dermatitis. These probiotics are taken orally and interact with the GI mucosa and gut-associated lymphoid tissue (GALT) that house over 70% of the immune cell inventory. These probiotics interact with macrophages, DCs of the mucosa and epithelial cells in multiple ways. Depending on the strain of bacteria, the probiotic can produce IL-12, IL-18, and TNF-α, or or have anti-inflammatory effects on the environment through releasing cytokines, IL-10 and TGF-β. These anti-inflammatory cytokines are fundamental in inducing immune tolerance in the skin (Dou et al., 2019).

Pathology (Microscopic View *Images) (Gross & microscopic)

Gross



Atopic dermatitis in an AA teenager showing scaly, lichenified, and dyspigmented areas of the cheek, back of the neck, inner arm, and forehead. (Taylor et al., 2011)



Hyperkeratotic cap in the stratum corneum stationed above the acrosyringium in the stratum spinosum of atopic dermatitis. (Miteva et al., 2017)

2. Acne (Vulgaris)

Incidence & Prevalence

Most of acne affects about all people from ages of 15-17 years and about 15-20% of all young people and 85% of people from ages (Law et al., 2010). The rates of prevalence was roughly about 40-50 million from a 1996 census survey. Luckey et al.'s study shown that the severity of acne in regard to puberty where half of the 10-11 year old boys had 10+ comedones (White, 1998). These comedones are one of the primary clinical diagnoses of acne vulgaris, including papules, pustules, nodules and cysts (Taylor et al., 2011). The team also noticed that 78% of girls between 8-12 years were afflicted with acne. The severity of the acne was shown to increase by progression of maturation in pre-pubescent young women. For young women, the levels were upregulated (Lucky et al., 1997). For the top three prevalent skin diseases, acne reigns as one of the top dermatoses. In the United States, United Kingdmom, France acne is one of the top dermatoses and now acne is also amongst the top dermatoses with the 2nd top skin disease. The levels were seen to be upregulated in these young women. Amongst the top three prevalent dermatoses, acne was identifed as one of the top three skin condition in the UK (Rea, Newhouse, Halil, 1976), France (Wolkenstein et al., 2003), and USA (Johnson & Roberts, 1978), and here, we see that acne is the same for West Africa. In West African skin, which is also skin of color, acne is primarily inflammatory (Dreno et al., 2015).

Etiology

Gram-positive P. acnes is normally found on the milieu of the pilosebaceous canal and mostly located in sebaceous areas and found on the skin. The bacterium's involvement is not as

clear as the understanding that P. acnes is not a pathogen for acne, if it were a traditional infectious disease. There are mainly four pathways that provide P. acnes the adequate inflammatory pathways in inflammatory acne. TLRs, inflammasome activation, MMP production, and antimicrobial peptides being stimulated. There are also different effects on the innate immune from different P. acnes strains but the adaptive immune system can be activated through the complement system and attack neutrophils via the C5 mechanism (Dreno et al., 2015).

Furthermore, with Th17 cells and P.acnes, there is an IL-17 response from the activated CD4 T cells, exerted by the anaerobic lipid-rich environment of the sebaceous follicles. As IL-17 is prevalent in acne lesions. Futher studies should examine the immunological profile of acne in patients with skin of color, and those of the West African populations/diaspora both clinically and epidemiologically. Additionally, the different phylotypes of P.acnes correlate to various pathogenic associations with non-inflammatory (comedones) vs inflammatory acne lesions. Studies found that this genomic variation of the phylotype IA shows an increase in inflammatory lesions, while the and phylotype IB Type II are decreased ((Nelson & Schneider, 2016).

Milk, dairy and fats are associated with the insulin-like growth factor binding protein and IGF-1 which connects the nutrient availability to mTORC signaling pathways in acne pathogenesis. The mechanisms of how food is a risk factor of acne vulgaris. The involvement of the insulin/IGF-1 signaling pathway demonstrates a process of food-induced activation. This activation of the axis triggers acnegenic effects that related to lipogenesis of the sebaceous glands. Milk products contain IGF-1 in addition to other the high-GI foods, fats, meat and dairy proteins that increase the levels of insulin and IGF-1. These levels of insuling and IGF-1 supply the mammalian target of rapamycin complex-1 (mTORC-1) and forkhead box O1 signaling pathways with nutrients to the acne-pathogeneis signaling processes (Norat, Dossus, & Rinaldi, 2007).

The pathogenesis has been controversial since the early 1900s. Studies have shown that the glycaemic index (GI), diet and prevalence of acne has been inconclusive. More recent research has shown that the emphasis of the mechanisms of high GI foods are correlated with lesional acne pathogenesis. A specific study focused on 32 acne-prone patients that are filled with a diet of carbohydrates and review of the course of 10 weeks. There was a 70.9% decrease of inflammatory lesion count in comparison to the baseline and smaller sebaceous gland size in

the lower GI diet group (Kaymak et al., 2007). From these studies, it is conclusive that there is lower activity and subsidized sebum production in acne vulgaris.

Risk Factors

In regards to the risk factors of acne, there is an axis between diet, genetics, and P.acnes. A 4-month case study reflects that people with acne and a higher GI diet consumed larger amounts of milk and ice cream compared with controls (Ismail, Manaf & Azizan, 2012). The amount of milk consumed related to acne is 3 or more servings of milk per week, but the amount is not identified for skim milk (Ismail, Manaf & Azizan, 2012), which is shown to have a higher correlation with acne (vulgaris) with a higher GI of 4 vs 3 (Foster-Powell, Holt, Brand-Miller, 2002). The dairy powerhouse, chocolate, shows that daily consumption of 50 g for four induced the release of the cytokine IL1β and IL-10 to further stimulate the P.acnes bacterium.

There are other theories that provied further explanation for the risk factors by way of a high GI diet. These theories provide way to give reason as to why indigenous populations of Papau, New Guinea have no acne in comparison to a Westernized diet and lifestyle such as in Belgim with prevalent acne (Cordain et al., 2002).

A genome-wide association study (GWAS) of European American teenagers with severe acne was conducted using the Nurses' Health Study II cohort. The chromosomal locus of 8q24 was found to be associated with severe acne amongst teenagers. As this locus has previous ties to prostate, breast, ovarian, colon and bladder cancers, and these ties can be correlated to is close proximity of the proto-oncogene Myc in addition to androgren receptor genes. The main qualm with this study surrounds the self-reported data collected with no objective assessments of acne (Zhang et al., 2014).

An additonal study discussed polymorphisms in cutaneous androgren genes which regulate genes HSD3B1 and HSD17B3 with increased susceptibility to developing acne vulgaris in this population. Comparatve genomic analysis of 82 P.acnes phylotypes which were isolates of the two levels of subject variables. The study concludes that phylotypes from the same individual are closely related to one another rather than related to phylotypes from different individuals (Yang et al., 2013). This is indicative of clonal expansion in the microbiomes' of participants. This may provide, after understanding the genetic compartents of P.acnes, comprehension of the difference between commensal bacteria in acne and in non acne skin.

Another study from the authors includes metagenetic analyses of P.acnes from 49 and 52 people with and without acne, which gave way to the discovery of P.acnes structures as they were different between the two groups in terms of key markers. This structural understanding provides insight as to how acne may vary between individuals. The genomic achievements of the human P.acnes genome has been incredibly useful in the development of molecular-based therapies, a fairly de novo area of acne treatments (Fitz-Gibbon et al., 2002) treatment.

Pathogenesis

Acne pathogenesis is known by hyperproliferation and abnormal differentiation of the follicles of the epithelium. It includes excess sebum production, proliferation of P.acnes in addition to formation. The inflammation that presents itself in lesional acne and microdomes. Immunohistochemical studies show higher levels of CD4 cells, macrophages and IL-1- alpha for patients with acne compared with skin of those without acne. These findings elucidate the idea that inflammation comes before hyperproliferation (Ingham et al., 1992). All acne is inflammatory. Studies have shown that higher doses of IGF-1 will develop acne as IGF-1 replacement therapy leads to acne and hyperandrogenism. There are multiple mechanisms of IGF-1 that lead to and induction of androgen synthesis, and activate the FoxO1 that allows for further androgen synthesis. This then increases the sebum triglycerides and fatty acid desaturation which led to more inflammation and comedogenic fatty acid profiles (Abulnaja, 2009).

Changes in the diet allow for sebum quantity to change and promote P.acnes overgrowth and gives room for the formation of biofilm. The P.acnes bacterium allows for the triglyceride lipase to increase palmitic and oleic acids levels, which lead to biofilm formation. The palmitic acid and P.acnes molecular patterns activte TLR2 and stimulates IL-1-beta signaling and inflammasome activation (Kim, 2002). The oleic acid allows for proliferation of keratinocytes, adhesion of the P.acnes bacterium, and IL-1-alpha release and formation comedones. Different phylotypes of P.acne have different phenotypes. P.acnes associated with acne induce high levels of IFN-γ and IL-17 in blood cells than those with non-afflicted skin. Healthy skin induces higher levels of IL-10, indicative of anti-inflammatory mechanisms at play in non-afflicated skin (McLaughin, 2019).

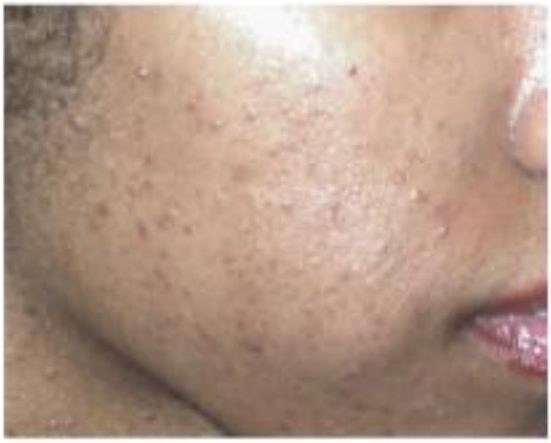
The key player in the innate system's role on the proinflammatory pathways. It activates TLR2 for monocytes and provides the release of IL-12 and IL-8. The cytokines IL-1 beat and IL-8 are secreted through the caspase-1 and nucleotide oligomerization domain-like receptor protein (NLRP) (Dreno et al., 2015) that . In regards to P.acnes, stimulates the adaptive systems through inducing the IL-17A and IFN-γ secretion from CD4+ T cells in vitro. TH17 cells and TH1 cells can react to the stimulation of P.acnes in patient cells that have a strong response to P.acnes (Kelhälä et al., 2014).

Propionibacterium acnes does activate TLR-2, TLR-4 on inflammatory cell membranes. The cytokines released are TNF-a, IL-1, IL-6, IL-8 and IL-12. The more severe acne is, the more cells will express TLR-2. This gives way to the cytokines that are created in proportion to P.acnes and it's interactions with TLR-2, defensins and MMPs (Dreno et al., 2015).

Milk, dairy and fats are associated with the insulin-like growth factor binding protein and IGF-1 which connects the nutrient availability to mTORC signaling pathways in acne pathogenesis. The mechanisms of how food is a risk factor of acne vulgaris. The involvement of the insulin/IGF-1 signaling pathway demonstrates a process of food-induced activation. This activation of the axis triggers acnegenic effects that related to lipogenesis of the sebaceous glands. Milk products contain IGF-1 in addition to other the high-GI foods, fats, meat and dairy proteins that increase the levels of insulin and IGF-1. These levels of insuling and IGF-1 supply the mammalian target of rapamycin complex-1 (mTORC-1) and forkhead box O1 signaling pathways with nutrients to the acne-pathogeneis signaling processes (Norat, Dossus, & Rinaldi, 2007).

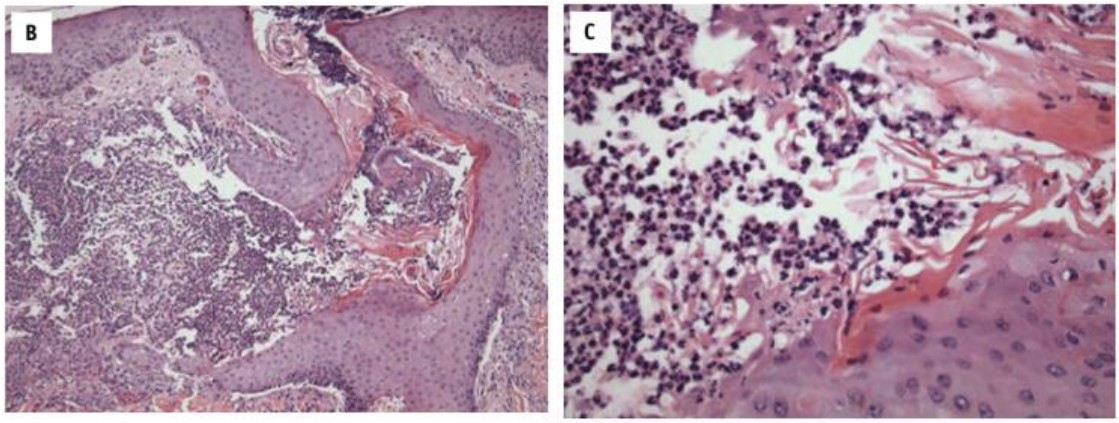
Pathology (Gross & microscopic)

Gross



Acne vulgaris in AA patient with post-inflammatory hyperpigmentation with pustules and papules. (Taylor et al., 2011)

Microscopic



Suppurative folliculitis that may be seen in any acneiform disorder such as with acne vulgaris. B,C show neutrophils surround and infiltrate the follicular epithelium, usually in large numbers typically present in large num- bers within the follicular canal. (Busam, 2010)

3. Urticaria

Incidence & Prevalence

The lifetime rate of incidence and prevalence for urtcaria ranges from <1% to 24% based on location, age, and sampling methodology (Anita et al., 2018). For women, acute and chronic urticaria is more common. For men, the ratio of urticaria compared to women is roughly about 1:2 (Sánchez-Borges, Capriles-Hulett, Caballero-Fonseca, 2015). For the eldery and young

children, the difference compared to women is less understood. In Europe, the lifetime prevalence ranges from 0.1% to 0.6% and chronic urticaria can progress in 20-45% of persons with initial acute urticaria. Studies have shown that for Americans, the period of prevalence for chronic urticaria was 0.08% while in Europe, data shows a prevalence range from 0.38% to 0.8%. For regular urticaria, the rate of incidence is lower (Lapi et al., 2016). For physical urticaria, the most common type is symptomatic demographism at 40%-73%, and the other solar and heat urticaria and angioedema tends to be a tad rarer. Beteween the ages of 25 and 55 years, the most common urticaria is chronic urticaria that tends to be there <2 years, and under 20% of the patients will have symptoms that last more than 10 years (Amsler, Soria, Vial-Dupuy, 2014). Patients with physical urticaria have a longer disease duration as 16% of patients had less than 1 year of symptoms. In general, urticaria is more popular in adults than in children. The prevalence amongst children is about 3.4% to 5.4% and for acute urticaria is from 2 to 73 per 100,000 emergency room referrals. As for chronic urticaria, the prevalence for children is 0;1% to 0.3% in the United Kingdom (Ferrante et al., 2015). As reported for West Africa, we calculated a signficant relative frequency of of 2.18% amongst the demographics tested over the course of the 20 years.

Etiology

There are a vast variety of causes of Urticaria that coincide with the type of clinical urticaria. As the dermatosis is primarily characterized by activation of effector mast cells and their rapid release of histamine, leukotrienes and prostaglandins. Medications such as penicillin, aspiring, NSAIDs, sulfonamides, oral contraceptives are a few on this developing list (Kayiran & Akdeniz, 2019). Foods such as nuts eggs, seafood, milk, fruits and vegetables can usually cause this condition in children (Rajan, Simon, & Bosso, 2014). Respiratiory allergens (pollen, mold spores, mites, hair and animal dandruff) (Chow, 2012), infections infections including parasitoses, contact urticarial (latex, cosmetics, and chemicals), insect bites, and psychogenic factors (stress and depression) can exacerbate the preexisting urticarial and induce further urticarial (Bülbül, 2015). Systemic diseases such as thyroid, rheumatic diseases, and carcinomas need to be monitored as deemed necessary in these afflicted patients. Pressure, heat, cold, and dermographism can manifest urticaria in less than 3-4 hours (Aktan, 2015). Urticaria can be hereditary as it is seen in agiodema and familial cold urticarial. Lastly, idiopathic urticarial can occur with out any known cause (Kayiran & Akdeniz, 2019)

Risk Factors

Acute urticaria is associated with a significantly higher risk of comorbidity with allergic diseases such as asthma and atopic dermatitis as well as a family history of allergic disease (Kjaer et al., 2008). Overall, patients with urticaria may fall ill commonly due to infection, food allergies, drugs, environmental changes and psychological factors. The chronic aspect of chronic urticaria is due to consistent triggering due to a specific stimulus aforementioned (Anita et al., 2018).

Upper respiratory stands firm as the main common cause of 40% of acute urticaria, drug reactions at 9.2%, and potential food intolerance at a low 0.9%. However, for the infectious agents, Mycoplasma pneumonia, parasitic infections and other upper respiratory tract organisms are more freqeuntly reported in children (Wedi et al., 2009). As for adults, viral helpatitisand infectious mononucleosis is more commonly reported in adults (Kulthanan, Chiawsirikajorn, & Jiamton, 2008).

Pathogenesis

The main cells involved in the pathogeneis of urticaria are mast cells and basophils (Borriello, Granata, & Marone, 2014) and their released mediators. These cell's activation can be caused by immunologic or non-immunologic factors. Mast cells and the basophils are the main cells involved in lesional urticaria driven by an IgE immediate hypersensitivity reaction. On the other hand, chronic urticaria shows about 30% of cases being associated with IgG antibodies and their iffinity to IgE receptors or IgA The vasodialator, histamine is released during degranulation during urticarial activity. Further activity of the disease includes increased levels of C-reactive protein, IL-6, IL-6 receptor, and MMP-9 (Dilek et al., 2016). The IL-6 medicated processes have an impact on the patient's sleep which are correlated to the severity of night symptoms of urticaria as concentrations of IL-6 and it's soluble receptor are upregulated during sleep (Kasperska-Zajac, Grzanka, & Damasiewicz-Bodzek, 2015).

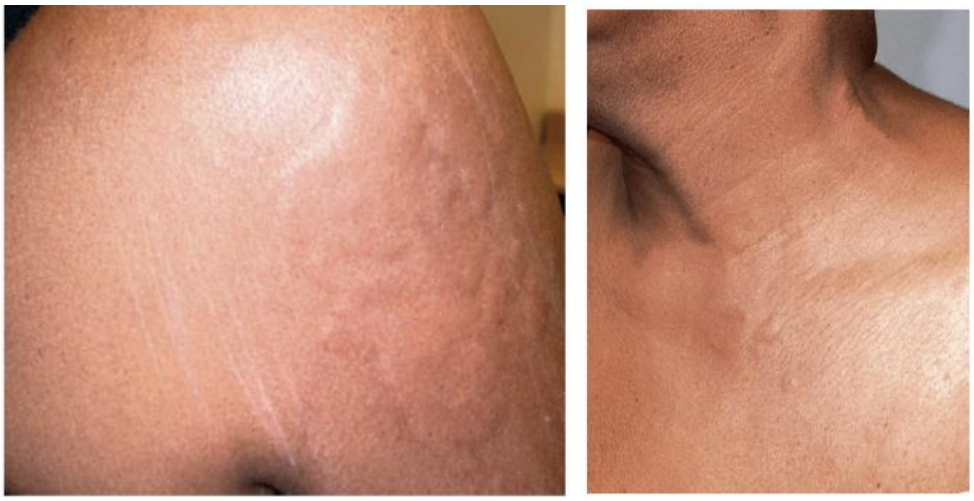
In relation to modulating the activation of mast cells, reactive oxgen species (ROS) are another apparent cause of mast cell degranulation in addition to cell signaling which helps the exocytosis of granules from mast cells. Of the complement system, the proteins C3a, C4a, and

C5a land on mast cells to help release histamines and function as anaphylatoxins (Ferrer, Nakazawa, 1999).

Adipokines can also impact immune responses in chronic urticaria The protiein lipocalin 2 and urticaria activity are negatively associated with one another, thus indicating antiflammatory properties of the adipokine in CU (Trinh, 2016). In all, these discoveries give a full image of the immunopathogenesis of urticaria with histamine release and mast cell activation at the foundation.

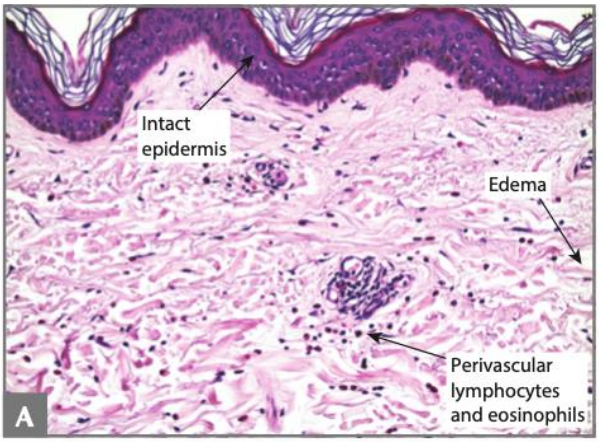
Pathology (Gross & microscopic)

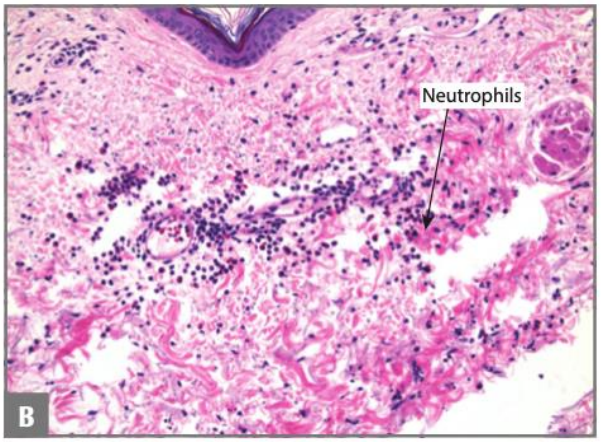
Gross



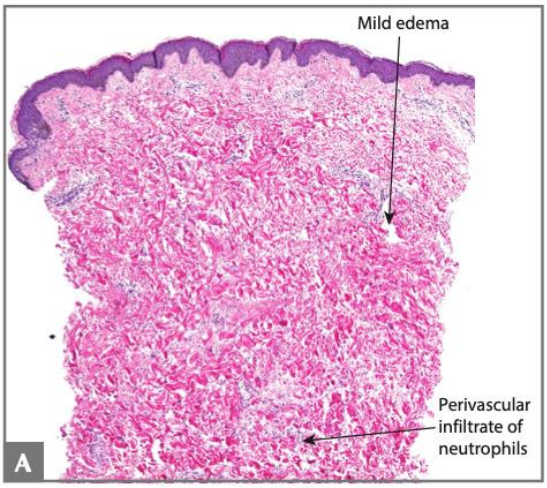
Chronic idiopathic urticaria wheals demonstrating superficial skin swelling surrounded by erythema (redness). This commonly lasts anything from a few minutes to 24 hours. (Taylor et al., 2011)

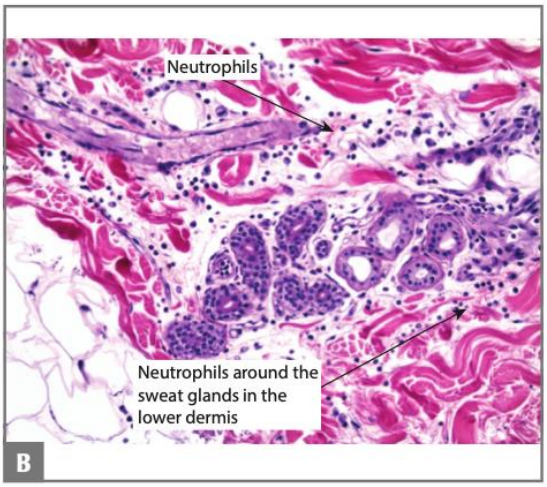
Microscopic



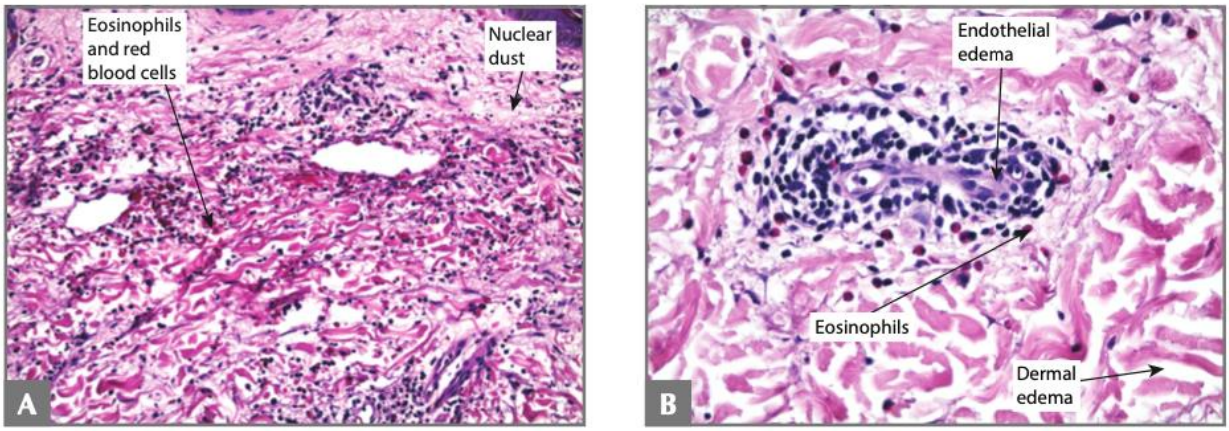


General urticaria with mild dermal edema (A) and margination of neutrophils (B) within post-capillary venules in acute urticarial. In later stages, a mixed inflammatory infiltrate of neutrophils, (perivascular) lymphocytes, and eosinophils are seen (A) (Miteva et al., 2017).





Neutrophilic Urticaria with mild edema in the dermis (A) and neutrophils rampage through the dermis and surrounds sweat glands in the lower dermis. (Miteva et al., 2017)



Urticarial Vasculitis showing eosinophil infiltrates amongst nuclear dust (A) in the dermis as well as dermal and endothelial edema (B). (Miteva et al., 2017)

4. Contact Dermatitis

Incidence & Prevalence [Population Most Affected]

There are two major subtypes that commonly are seen in patients, irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD is a nonspecific reaction on the skin due to a single instance or a repetitive exposure to a substance in contrast to ACD that is an immunologic response to antigens upon contact while being categorized as a delayed hypersensitivity reaction (Litchman, Nair, Atwater, 2019). There is no specific age as where contact dermatitis will occur. The prevalence estimates range from 1.7% to 6.3% in a variety of published studies. In West African skin disease we reiterate a significant relative frequency of 2.94%. As many of our studies do not differentiate between urban and rural areas and gender, CD is more common in urban locations while being frequently seen in women and the eldery (Statescu et al., 2011).

Etiology

There are a plethora of substances that can cause irritant dermatitis, on the contrary, it is the concentration and the duration of contact of the agent at hand that can determine the chances of irritant contact dermatitis. The cause of contact dermatitis is formed by contact allergens or irritant substance. It is characterized by the eczematous eruptions that are at the start of a multitude of dermatologic conditions (Hamstra et al., 2015). Common causes of irritant contact dermatitis include solvents such as xylene and alcohol, rubber gloves sodium lauryl sulfate (commonly seen in shampoos), metal working fluids, alkalies, hydrofluoric acid, and even

plants! Not only can harsh irritants be the cause of this condition, a repeated exposure to mild irritants, such as water and cleansing gels, can initiate a form of ICD known as cumulative ICD (Karono & Maibah, 2019). The main allergens in allergic contact dermatitis are nickel, which binds to TLR-4, cobalt, fragrance mix, thiomersal, neomycin, and formaldehyde (Schmidt et al., 2010). The dust mite allergens Der p 2 and Der f 2 are homologs of the protein MD2 that binds to TLR-4 in ACD. These dermatophagoides subspecies consume keratinocytes and can be found on clothing, bedding and the skin (Shane, Long, Anderson, 2019).

Risk Factors

Although we do see women and the elderly as frequent victims of CD, age and sex alone cannot determine complete risk factors for this eczematous dermatosis. The occupational and home activities that frequent women and the elderly's daily lives can give rise to the higher rates of incidence (Statescu et al., 2011). Occupations are the number one risk factprs of acquiring CD as a whopping 80% of these skin conditions amongst occupations are irritant contact dermatitis. Susceptible populations include those with an atopic diasthesis in contact dermatitis (Litchman, Nair, & Atwater, 2019). There are, of course, environmental factors of dry air amongst high temperatures as seen in climates closer to the equator and warmer summer seasons. These factors can increase the potency effect of the contact agent.

Pathogenesis

Allergen-to-skin contact initiates the pathogenesis of ACD. This allergen passes through the stratum corneum where Langerhan cells migrate upward to local lymph nodes, and allergens present themselves to T cells. This is denoted as the 'sensitization' phase. These T cells then generate various cytokines such as IFN-γ that induce the inflammatory storm aforemention. It is important to not that only patients whom have been previously been sensititzed and produced specific T cells to the allergen can develop ACD (Richard and Harris, 2014).

Allergy is the phenomenon known to ilicit a hyperactive immune response to an allergen. Allergic contact dermatitis occurs after immediate exposure to chemical or nuance environment. This mainly results in the production of neoantigens due to haptenization and generating modified-self immunogenic antigens (reviewed by Kaplan et al. 2012). These haptens induce oxidative stress in keratinocytes by releasing reactive oxygen species and ATP that speeds up the

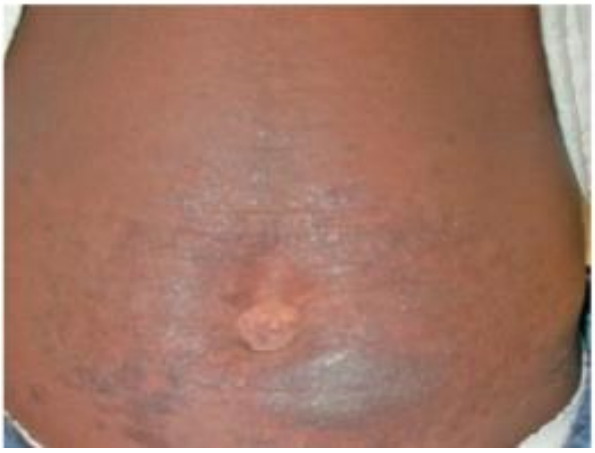
sensitization process. These immunogenic antigens can even be byproducts of the degredation of hyaluronic acid and active the important TLRs and producing proinfllammatory cytokines by tissue resident immune cells. Research shows that TLR-2 and/or TLR-4 in IL-12 dependent/independent pathways mediates the recognition of these neoantigens. The repeated exposure to the allergen induces the consistent type IV hypersensitivity reaction and sensitization. This is depicted by a large influx of T cells to the epidermis which induces detrimental tissue damage and an inflammatory storm (Richard and Harris, 2014).

The dust mites cause allergic responses that induce IgG and IgE responses for hypersensitivity reactions regardless of the immunity these antibodies provide. The dermal/epidermal resident mast cells will degranulate after they are bombarded with surface-IgE upon encountering an allergen. Avoidance of contact with the allergen is the preferred form of treatment (Richard and Harris, 2014).

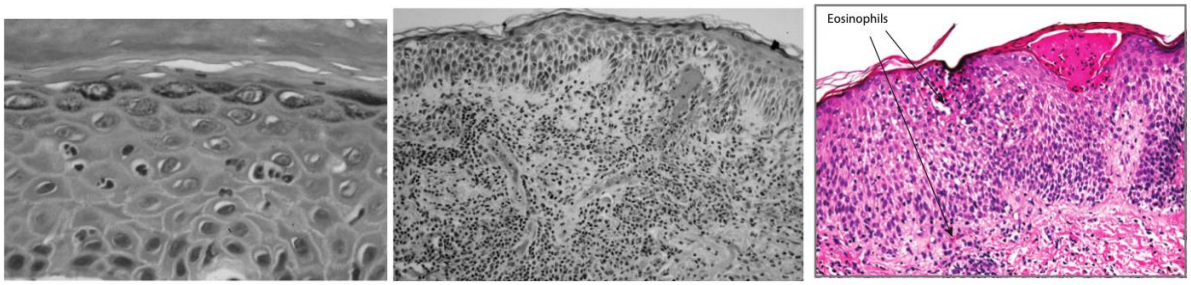
Irritant contact dermatitis involes impairment of the skin's barrier, changes in the epidermal cells and proinflammatory cytokine release such as IL-1α, IL-1β, TNF-α, IL-6, and IL-8. Keratinocytes release these mediators as a reaction to the chemical stimuli from the irritants, thus reigning as primary pathogenic factors for ICD. There is no need for prior sensitization for development of irritant contact dermatitits (Lee et al., 2013).

Pathology (Gross & microscopic)

Gross



Allergic Contact Dermatitis (ACD) in AA child due to nickel in a metal button on denim jeans. Black patients normally contract ACD from contactants such as PPD, nickel, chromates, and mercaptoben- zothiazole. As seen above, this dermatitis is often complicated by hyper-pigmentation and lichenification unless treated early and vigorously with systemic corticosteroids. (Taylor et al., 2011)



Irritant contact Dermatitis and photoallergic contact dermatitis show eosinophilic spongiosis in the epidermal layer of the skin. (Miteva et al., 2017)

5. Seborrheic Dermatitis

Incidence & Prevalence

For immunocompetent adults, sseborrheic dermatitis (SD) has a prevalence and incidence rate of 1% - 3% of the population while being more common in men than in women (Gupta & Bluhm, 2004). As for infants, SD occurs normally within the first three months for this population, in addition to occuring in adolescents and young adults. The rate of incidence grows further for patients over the age of 50 (Rosso, 2009). A previous cross-sectional case studies have evaluated over 2,035 patients in Greece and showed a total prevalence of 4.05%. A pediatric study in that same country showed that Greek children aged 0 to 15 years had a lower

relative prevalence (2.5%) than in Indian (11.3%), Chinese (3.2%) children (Sardana et al., 2009). For this rate was 4.05% yet lower than British and Chinese populations at 2.35% and 7%, respecctively (Goh & Akarapanth, 1994). The relative rate of incidence for West Africa is 2.50% and comparatively is higher than the Chinese adult population aforementioned.

Etiology

As there is not a definite image of the etiology of SD, the speculation surrounds Malassezia furfur as the organism of selection. This saprophytic fungus is the main cause of Tinea versicolor, a common dermatosis caused by an infection of the skin that leads to changes in pigmentation of the trunk and upper arms. SD has a multitude of etiological layers that include endogenous and exogenous factors for the development. Due to the knowledge that men do encounter SD more often, outside of infants, this develops mainly during the onset of puberty. This is suggestive of there being a hormanal component of the etiology of the disease, due to androgens. At this pubescent age, sebaceous glands are most active, providing reason as to why the lesions in SD are frequented in sebaceous gland-dense areas (Schwartz, Janusz, & Janniger, 2006).

Furthermore, a Malassezia infection has a pathogenic role in SD due to the positive correlation between yeast population density and SD severity of the skin. This theory s further supported by the highly effective antifungal therapy in SD (Gupta & Bluhm, 2004).

Risk Factors

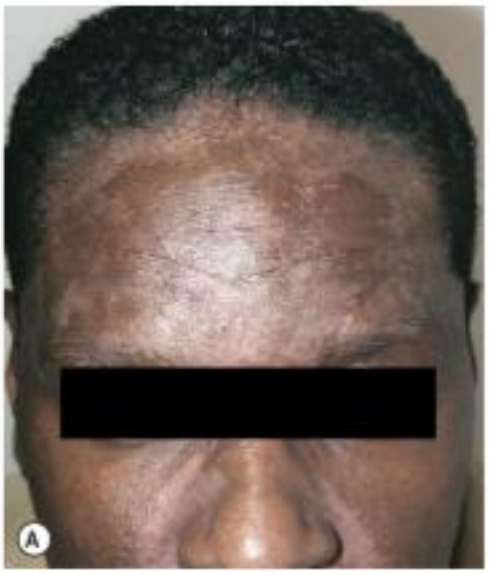
Immunocomopromised and immunosuppresed patients such as orgran transplants recipients, HIV/AIDS patients, patients afflicted with the hepatitis C virus, and other immunosuppressive ailments (Lally et al., 2010). This population's rate of incidence being a floundering rate of 83% in comparison with the vastly lower 1%-3% rates of the general public, which indicates the importance of immunity in the pathogenesis of this disease (Faergemann et al., 2001). SD is also more common amongst patients with neurologic and psychiatric diseases, such as Parkinson's disease and mood depression as well as patients with genetic disorders such as Down syndrome (Ercis, Balci, Atakan, 1996).

Pathogenesis

The humoral and cellular immunity has had a bit of contradictory results, where one study (Keiffer et al., 1990) found a low-level of the CD4+/CD8+ cell ratio in 68% of patients versus a study where another study (Ashbee et al., 1994) found a regular, standard ratio in all the patients with SD. An additional study discovered that there were normal levels of CD4+/CD8+ cells but a lower number in roughtly 28% of patients with an increase of natural killer cells in 48% of patients. The varying increased and decreased levels of the immune cell population indicate battered cellular immunity. The adjsted CD8 T cell counts have reflected a cytokine release (Faergemann et al., 2001). The Malassezia yeast lowers the production of pro-inflammatory cytokines that relates to the presence of the microfibrillar layer around yeast cells. This high amount of lipids extracted amongst the cell walls been demonstrated in studies to reverse the capacity of reduction of pro-inflammatory cytokines thus preventing the induction of inflammation (Kesavan, Holland & Ingham, 2000). In SD, this yeast does too fall short of having a consistent lipid layer and gives potential reason to the inflammation in the disease (Prohic, 2009). The Malassezin and indole-3-carbaldehyde are ligands that have implications in immunologic occurences such as the differentiation of TH17 cells which were only produced on the skin of patients of SD M restricta (Gaitanis et al., 2008).

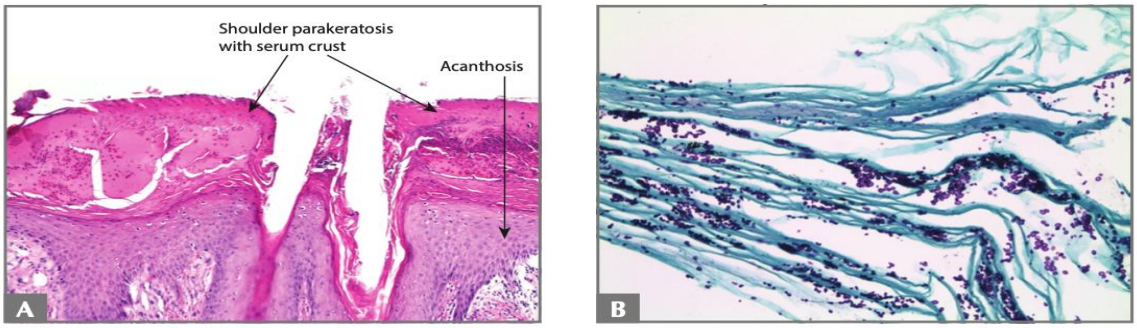
Pathology (Gross & microscopic)

Gross



Sebhorreic Dermatitis usually has ill-defined greasy soft scale involving the scalp, and nasolabial and retroauricular skin folds. The picture shows aforementioned hypopigmented and scaley patches by the nasolabial folds and hair line in AA male. (Taylor et al., 2011)

Microscopic



Seborrheic dermatitis seldom requires biopsy. In photo A, seborrheic dermatits of the scalp demonstrating shoulder parakeratosis with serum crust in the stratum corneum. Note the acanthosis in the spinous layer B. Pityrosoporum of the parakeratotic layer of SD (yeast as the 'spaghetti' fibers and spores). (Miteva et al., 2017)

6. Human Papillomavirus (Viral Warts)

Incidence & Prevalence

In the US, there are roughly 14 million new human papillomavirus (HPV) infections with about 79 million individuals currently infected (CDC, 2020). The spread of HPV occurs through

skin-to-skin sexual activity and is prevalent in all populations that are sexually active. The CDC estimated that at least half of all sexually active individuals will contract HPV at some point, and at least 80% of women will acquire the HPV infection by the age of 50 (CDC, 2004). In the US, roughtly 10% of the population is estimated to have active HPV infections, 4% has the infection that caused cytological abnormalities and 1% has an infection that is the source of genital warts (Koutsky, 1997). The calculated rate of relative prevalence for West African HPV is 1.85%.

There are oncogenic HPV strains (commonly strains 16, 18, 31, 33, 35, 39, 45, 51, 52, and 58) associated with anal, cervical, vaginal, and vulvar cancers, in addtion to non-oncogenic and low-risk cancers (6, 11, 40, 42, 43, 44, and 54) which are associated with genital warts (Muñoz et al., 2003). The most common and oncogenic type is HPV 16 with an infection rate of 10.4% and for HPV 18 with an infection rate of 4.1% for the same 2-year period (Brown et al., 2005). Studies have shown that women who have sex with women are not immune to HPV as their DNA has been found in both low-risk and high-risk HPV (Marrazzo et al., 2001). HPV 16 is notable connected to over 50% of cervical cancers (Stone et al., 2002), so understanding this form of HPV is of preferred focus. A study reviewed the HPV 16 antibodies that demonstrate prior exposure to HPV rather than the viral DNA load from frequent tests, and found that women were more likely to be seropositive for HPV 16 (17.9%) than men (7.9%). Au contraire, the method slightly undermines the prior exposure to HPV 16 as <60% of women with HPV 16 devlop the specific antibodies (Ault, 2006). HPV 6 and 11 are the common subtypes correlated with genital warts and roughly 90% of the lesions (Braaten & Laufer, 2008).Of the 1% of Americans that do have genital warts, there are 13% of those persons that have attended STD clinics that do have visible genital warts. Winer et al looked at 148 female college students when they began sexual activity, and found a cumulative incidence of HPV 38.9% after 2 years, when the infection normally clears (Winer et al., 2003).

Etiology

Among the 180+ varying strains of HPV, this virus houses itself with the papillomaviridae family of noneveloped DNA viruses. The HPV infects keratinocytes by overriding the cell's machinery to devlop progeny viruses. The keratinocyte differention is then connected to the HPV replication cycle where proteins early ("E" 1–7) are generatied in non-differentiated keratinocytes while late proteins ("L" 1 and 2), that are associated with capsid

formation are generated to support the sloughing of the HPV. Some HPV strains can be transmitted through sexual contact and cause genital warts or warts on other part of the skin. The subtypes of HPV are 1, 2, 4, 27, result in cutaneous warts of the hands and feet as with verruca vulgaris or verruca plantaris (histology images 1 and 2). Moreover, locations where HPV is found relates directly to the strain. Strain 1 normally infects soles of the feet, strain 2 infects the palms of the hands, strains 6 and 11 are the cause of genital warts, strains 16 and 18 are connected causing cervical cancer. There have been two vaccinces developed for HPV: Gardasil for types 6, 11, 16, and 18) with the aim to prevent cervical cancers (Richard and Harris, 2014).

Risk Factors

The main risk factors for HPV infection depend on the strain of HPV. Overall, risk factors are sexual activity, gender and age of first sexual intercourse, smoking, use of oral contraceptives for longer than 5 years, chewing betel nut, and exposure to radiation and UV light (Luria & Cardoza-Favarato, 2020). The highest rates are consistnetly found in sexually active women under the age of 25 (Ault, 2006). Sexual activity ranks as the main risk factor for HPV infection, as condoms are useful for preventing a multitude of sexually transmitted diseases, but can still leave users susceptible to varying HPV infections. A recent meta analysis reviewed over 20 trials that reviewed the relationship of condoms and HPV infections. The study concluded that condoms do protect against some HPV-related disease, they do not protect against cervical infections (Manhart & Koutsky, 2002).

Pathogenesis

The antiviral immunity to HPV is dependent upong the NK and CTL immune responses (Galluzzi et al., 2012). The two cell populations anihilate their targeted proteins through perforin/granzyme-led apoptosis. The immune response for the majority of viral infections include the obliteration of virally infected cells alongside minimal inflammation which reflects little to no redness, swelling or pus that is seen commonly with bacterial or fungal infections. TH1-based cytokines are key in HPV (and viral overall) immunity due to their acceleration of CTL reponsses and production of IFN-γ that provide an antiviral effect on the mechanisms at hand (Stevanović et al., 2015).

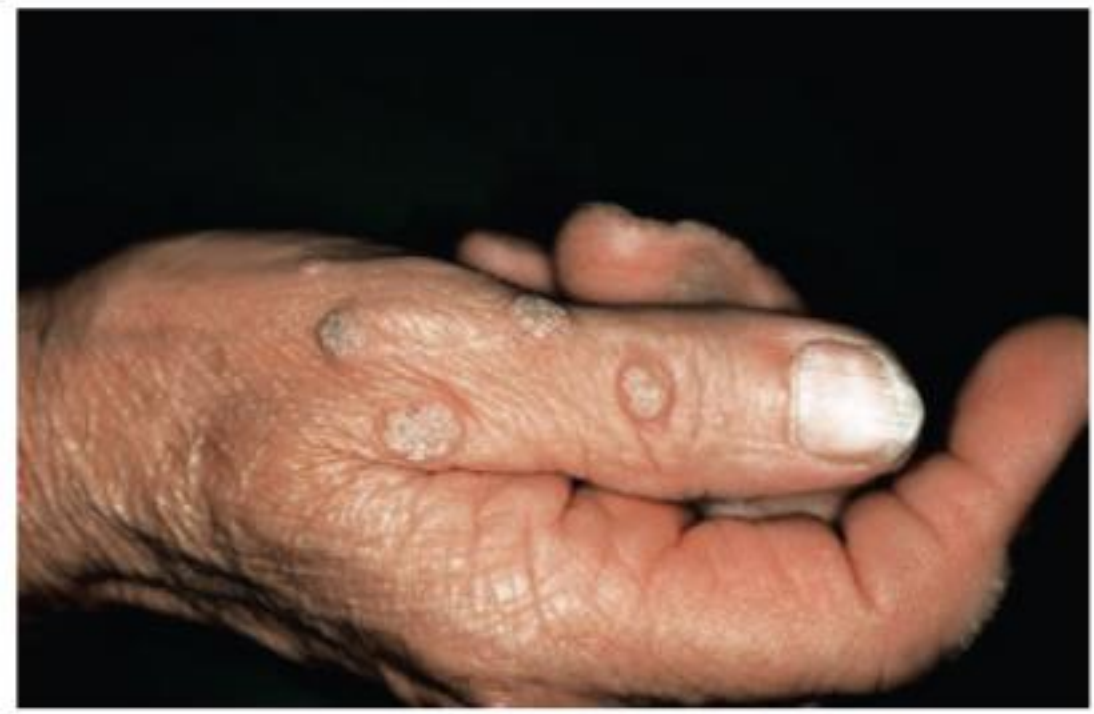
The proteins E6 and E7 of HPV will inhibit p53 and Rb, respectively, and are good for sensing damaged DNA and repair mechanisms to prevent cell-cycle progression (Grabowska & Riemer, 2012). Through protosomeal degredation by way of ubiquitin, E6 and E7 can inihibit these 'genome guardians' and obstruct the health of the genome and influence improper growth. This generates the byproduct of hyperproliferation of keratinocytes to manifest a wart. The HPV also avoids antiviral responses regulated by IFN-γ through the E7 protein. This protein can also inhibit the promoters of type-I IFN-related genes. It is this reason as to why IFN-alpha is an option for treatment of genital warts although patients with high E7 levels have a lower response rate than patients with low E7. The E6 protein downregulates IL-18 expression that induces TH1 and CTL immune responses (Richard & Harris, 2014).

NK cells in productive antiviral immunity search for the presence or absence of self HLA I on cell surfaces, while CTLs in productive antiviral immunity respond to direct HLA-I-peptide complexes. With that, HPV's E5 protein harnesses the ability to downregulate HLA I expression by inhibiting tapasin protein and the HLA I promoter binding through transcription factors (de Freitas et al., 2017). As the E5 protein lowers the chance of a CTL killing an HPV-infected cell, a NK cell still can harnesses the opportunity to do the same. NK cells use their killer activating receptors (KARs) and killer inhibitory receptors (KIRs) to dectect HLA I presences on cellular surfaces (de Freitas et al., 2017). Although the balance of positive and negative signals provide the NK cells to target the virally infected cells, not many of these populations result in getting recruited to the target cell. The virus has sequestered itself inside the highly-localized and differentiated keratinocytes of the epidrmis (Richard & Harris, 2014). It is because of the superficial keratinocytes that antibody responses are mitigated in HPV due to little to no secretion of immunogenic L proteins in quanitites large enough to muster maturation of APCs, secrete cytokines and promote effector T-cell activitaiton. Some LHC and APCs can take up HPV antigens through phagocytosis or through exosomes, but as HPV is not very inflammatory, this occurrence is uncommon (Tindle, 2002).

Within the HPV wart, the Langerhan cells produce the CC chemokine ligands CCL17 and CCL22 that carries the recruitment of CD4+ CD25+ FoxP3+ Treg cells. These Tregs have the ability to lower inflammation and contribute to the survival of the HPV and also have been identified in patients with cervical cancer (Richard & Harris, 2014).

Pathology (Gross & microscopic)

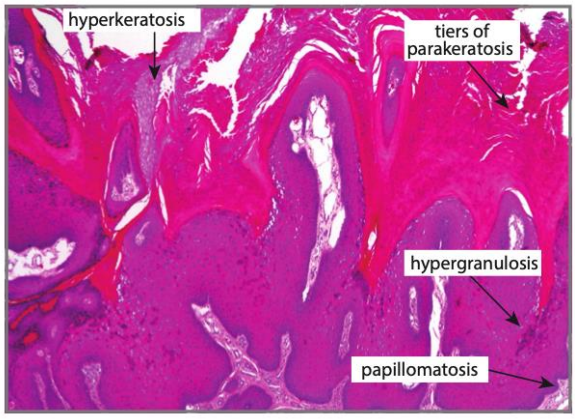
Gross Pathology

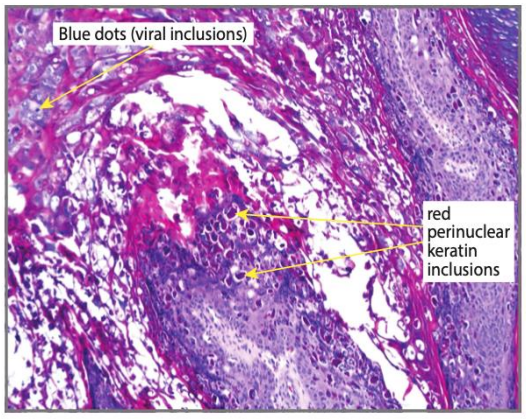


Verrucae vulgares type keratotis warts are shown from a patient diagnosed with HPV. The anogenital wart of Human papilloma virus, which is traditionally known as the condyloma acuminata, serves as a soft, pink, pedunculated papilliferous mass. These masses have a pointy and fissured surface that can develop into cauliflower-like lesions in pregnant or immunosuppresed patients. (Taylor et al., 2011)

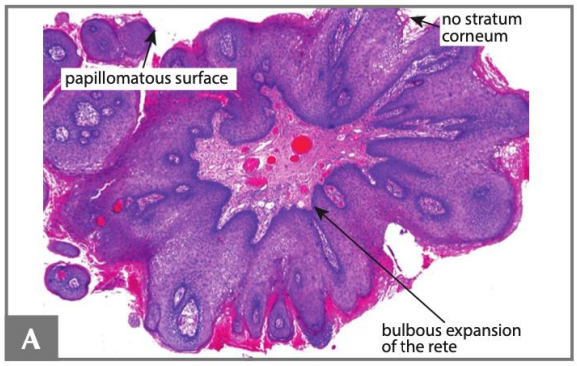
Microscopic

The microscopic and wart histology can reveal hyperkeratosis, papillmatosis, and parakeratosis.

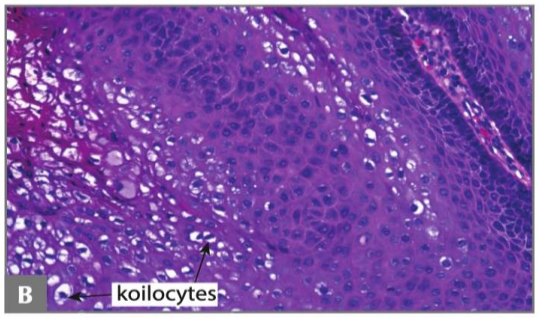


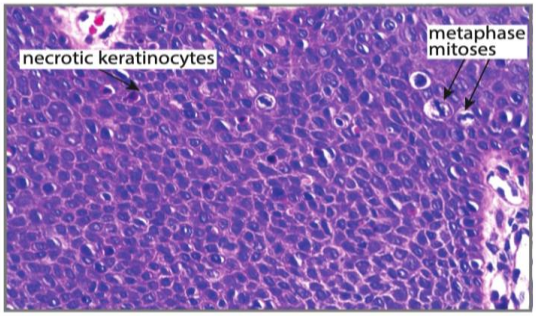


(Left) Verruca vulgaris. The lateral rete point toward the center of the lesion. (Right) The plantar wart histology demonstrates viral inclusions as the blue dots seen throughtout the slide in addition to red, perinuclear keratin inclusion in the skin. (Miteva et al., 2017)

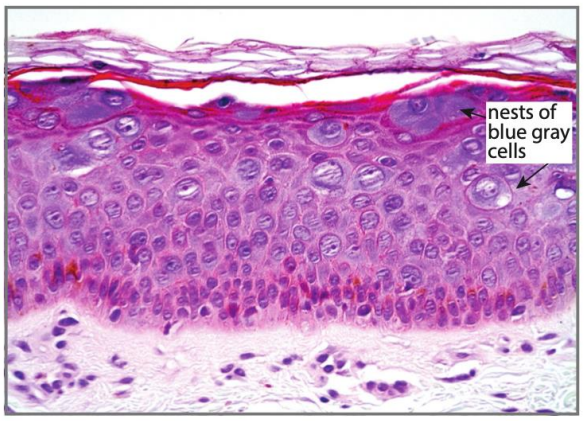


Bulbous endo-exophytic acathosis demonstrates a papillomatous surface with the bulbous expation of the rete, resembling the branches in a cauliflower. (Miteva et al., 2017)





(Left) Condyloma acuminatum. Koilcytes in an HPV lesions appear as shrunked raisin-like nuclei. (Right) Bownenoid papulosis. The epidermis takes a ‘windblown’ appearnace due to the croweded and atypical keratinocytes, necrotic kerantinocytes and increasd metaphase mitoses. (Miteva et al., 2017)



Epidermodylsplasia verruciformis (EDV) with blue-grey cells showing a perinuclear halo in the stratum spinosum and straum granular layer in verruca plana. (Miteva et al., 2017)

7. Vitiligo

Incidence & Prevalence

Vitiligo remains the most popular disorder of pigmentation. As India is representative of the most frequent cases of a whopping ~9%, the US' incidence rate is roughly 1%. In Denmark, this disease is studied widely in Denmark, with the largest study orchestrated in 1977, resuting in an incidence of 0.38% (Howitz et al., 1977). As of 2012, 1% of the world population is affected by vitiligo (Ezzedine et al., 2012). This disease does not favor any specific gender, however, more women will address discomfort with their condition, as vitiligo can be categorized as a cosmetic problem. Although this condition can arise at any age, ~75% of cases can develop by the age of 30. More commonly, this skin disease arises by the age of 12. Vitiligo can develop at any age. However, in 70%–80% of cases it arises before the age of 30 (Alikhan et al., 2011). Furthermore, an onset before the age of 12 years is common, affecting up to 37% of patients (Richard and Harris, 2014).

Etiology

As there is no exact known cause for vitilitgo, there is the autoimmune hypothesis that sits at the foundation of etiology for vitiligo. Other oxidative-stress reated, cytotoxic theories and neruohumoral ideals are not supported with much solid evidence. The recent hypotheses are surrounding decreased melanocyte survival amd melanocytorrahagy. As many biologists seek to understand the source of melanocyte destruction and their subsequent loss in damaged skin, the

likelihood of all the supported aforementioned theories playing a role in the etiology is high (Alikhan et al., 2011). The convergence of these theories add stress, autoimmunity, mutations, acculumation of compound toxicity, and impaired migrtion of melanocytes in the epidermis' basal layer (Le Poole et al., 1993). The autoimmune theory is related to the generalized vitiligo while neurohumoral hypothesis (with limited evdience) is related to segmental or focal vitiligo (Hann & Lee, 1996).

Risk Factors (Genetic)

Genetic abberations are the main players in vitiligo. There are, on average, about 50+ genes that are conncted to vitiligo. However, only a few of these genes demonstrate a straight link to the dermatosis. The non-HLA genes DDR1, NLRP1, XBP1, PTPN22 and COMT (Njoo & Westerhof, 2001). The HLA genes associated with vitiligo are HLA-A2, HLA-DRA4 and HLA-DR7 alleles (Singh et al., 2001). The DDR1 gene on locus 6p21 is included into adhering melanocytes to the stratum basale through the CCN3 integrin protein (Silva de Castro et al., 2010). This mutated gene downregulates the adhesion of the cells carrying the melanocytes in the basal membrane. Next up, the XBP1 gene on the locus 22q12 can be interruped amidst MHC II genes with recent studies indicating elevated levels of XBP1 in lesional skin of vitiligious patients as carriers of this gene (Ren et al., 2009). The risk of generalized vitiligo is correlated to a plethora of variations of NLRP1 on the locus 17p13. Interestingly enough, this gene was first to be correlated with American families afflicted with vitiligo (Jin et al., 2007). Additionally the PTPN22 gene located on locus 1p13.3-p13.1 is identified as risk factor to generalized vitiligo (LaBerge et al., 2008). Finally the COMT gene on the chromosome 22q11.1-q11, relates to oxidative stress in vitiligo because of its ability to metabolize catecholamines. In all, these genes produce the risk of developing vitiligo (Türsen et al., 2002).

The last key genetic indicator involves on upwards of 20% of patients with vitligo that have a first degree relative afflicted with vitiligo. The relational risk increases by ten-fold with patients that have a first-degree sibling with vitligo (Iannella et al., 2016). In African Americans, the HLA haplotype that is elevated in this population is the DR4, DQw3 (Dunston & Halder, 1990). Current studies to elucidate this HLA haplotype in West African population should be further elucidated.

Pathogenesis

Vitiligo is an autoimmune disease that destroys melanocytes from the epidermis, affecting patients psychologically on a large scale. There is no preference for gender nor race but the disease does prefer the face and genitals, hands and feet, trunk and proximal extremeties. The depigmented patches are normally symmetrical outside of segmental vitligo. This vitiligo affects about 5% of the global vitiligo patient pool and it's depigmentation is unileratally localized, restrited to the midline/body's spine. This is also the main vitiligo for adolescent patients. Amongst all vitiligo paitents, there are occasional complaints of itching of the skin's lesions (Taieb & Picardo, 2007)

This dermatosis is IFN-γ and CTL mediated that is led by a TH1 immune response within the dermis. Generally speaking, the majority of autoimmune diseases are difficult to assign specific antigens that respond to autoreactive T Cells. The T-Cell receptor in vitiligo is determined by specific proteins such as the melanoma atnigen recognized by T- Cells, MART-1/Melan-A, tyrosinase enzyme that is widely known in melanin production, and gp1000, the premelanosome transmembrae protein on the surface of melanocytes (Palermo et al., 2001).

From histology and clinical representations, vitiligo resembles antitumor and viral repsonse as seen in psoriasis. With that, treatments for this condition resort to anti-TNF-alpha inhibitors but with little to no avail. Traditional everyday treatments are topical steroids and calcineruin inhibitors administered through narrow-band UVB light therapy (Schallreuter et al., 1999). Currently, emerging therapies utilize IFN-γ with additional TH1 inflammatory pathaway mechanisms (Richard and Harris, 2014).

The autoimmune regulator (AIRE) is generated in the thymus through specialized cells and induces (in vitiligo's case, epidermal) self-antigens to give way for negative selection of autoreactive T cells as they develop. When missing this protein, patients are unable to delete autoreactive T cells that attack the patients own immune system and leads to a conglomerate of autoimmune dermatoses with vitiligo on the list (Tazi-Ahini et al., 2008).

As the role of anti-melanocyte antibodies in this condition requires further elucidation, high levels of autoantibodies have been found in the periphery of 10% of vitiligo patients, against tyrosinase one (TRP-1) and tyrosinase two (TRP-2) (Kemp et al., 2011) A vast majority of papers demonstrated CD4+ and CD8+ T chells in the DEJ (dermal-epidermal junction) of skin surrounding vitiligo lesions, magnifying cell-mediated immunity's activation in vitiligo (Zhou et al., 2012) (Oyarbide-Valencia et al., 2006). Another recent study looked into the presence of

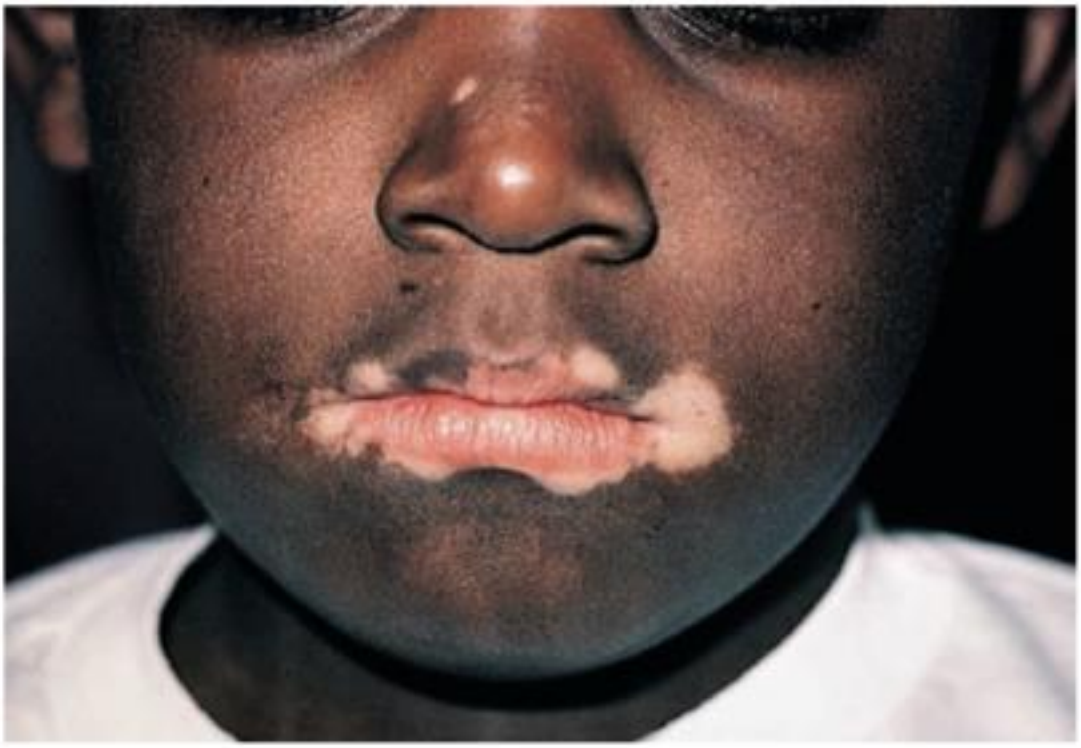
CTL that anhiliate melanocyts in skin surrounding vitiligo lesions (van den Boorn et al., 2009), and elucidated that HLA-A2 restricted, melanocyte-specific T cells in vitiligo patients are correlated to activity of the dermatosis (Lang et al., 2001). Additionally, TREGS have been shown in reports to be fundamental in the pathogenesis of vitiligo. When TREGs are reduced in the peripheral blood, their lack of uniform acticity increases damage to melanocytes (Dwivedi et al., 2015).

Specific cytokines have been reviewed in vitilgio, as this has been categorized as a TH1 diseases. The increase of TNF-alpha, which gives reason for the lightly effective anti-TNF-alpha inhibitors, IFN-γ, IL-10, and IL-17, which has been found in blood and tissue of vitiligo patients, are the main cytokines involved in vitiligo (Speeckaert, Speeckaert & van Geel, 2015). Specifically, the activity of IL-17 has in inductive effect on the production of TNF-alpha, which adds to the cascade of persistent behavior in this dermatosis (Bassiouny & Shaker, 2011). Although there have a variety of pathogenic theories to elucidate the loss of self-tolerance in vitiligo, there needs to be further understanding for optimal treatments.

Pathology (Gross & microscopic)

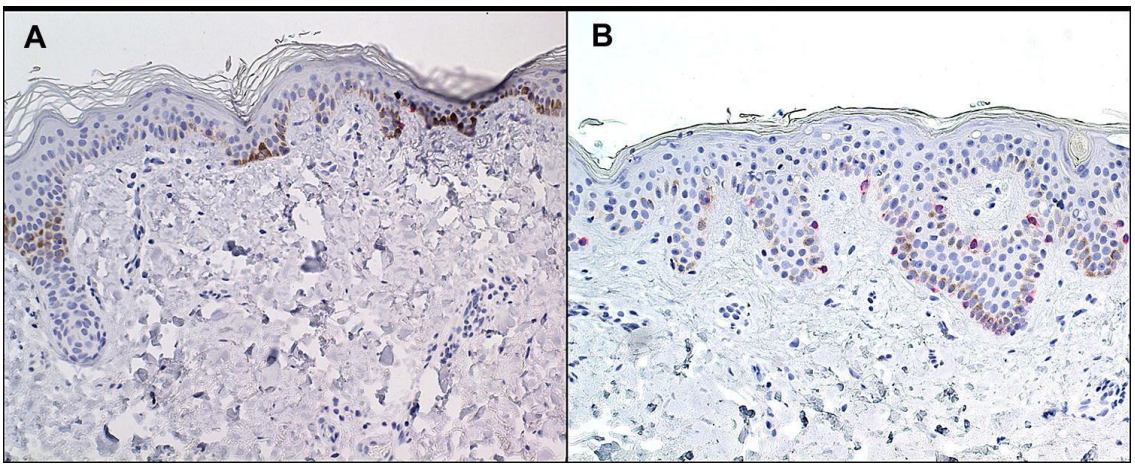
Vitiligo is characterized by the physical findings in the DEJ and this can be helpful in diagnosis of the disease. There are absent melanocytes with negligible inflammatory cells infiltrating the tissue. Any active lesions may have a lichneoid presentation. Immunohistochemical stains confirm this absence with melanin granules within keratinocytes (Gokhale & Mehta, 1983). The melanocytes on the edge of vitiligous skin are often vaculolated with many dendritic processes filled with the granules of melanin (Moellmann et al., 1982).

Gross

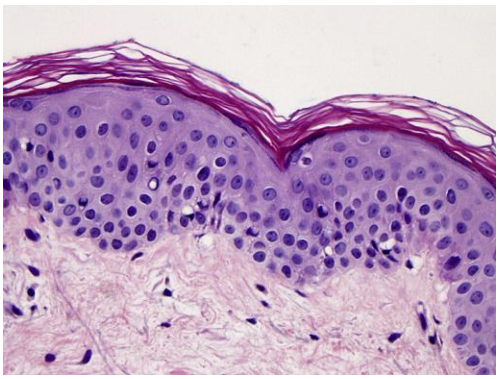


Perioral vitiligo on a young African American boy with macules and patches of skin around the mouth with a lack of pigment. This can be classified as a type of segmental vitiligo as it appears in unisegmental portions around the mouth. (Taylor et al., 2011)

Microscopic



Vitiliginous skin (A) houses with only two pan melanoma cells vs unaffected skin (B) with many basal keratinocytes that have signficant melaning pigment in them. (Panmelanoma cocktail stain [HMB45 + tyrosinase + MART-1; Biocare Medical, Concord, CA].)



We see a slight ridge pattern with suprabasal vacuolization and occasional suprabasal clear cells. There are little to no inflammatory cells in the dermis with no melanin visible. (Hematoxylin–eosin stain; original magnification: ×30.)

Table 5: Cytokine-Related Immunopathogenesis of West African Dermatoses.
The table below includes the 7 statistically signficant diseases and their immune profile including cytokines, immune cells, and mediators. As developing immunotherapies are fairly de novo in treatment of disease, identifying multi-axis mediators proposes treatments that can be utilized.

Skin Disease	Immunopathogenesis
Atopic Dermatitis	IL4, IL-5, IL-13, , IL-17, IL-23 induced TH2 cytokine release, TH1 cytokine release
Acne Vulgaris	IL-1-alpha, IL-1-beta, IL-12, IL-8, IL-18, IL-17A, IGF-1 increase
Contact Dermatitis	IL-1-alpha, IL-1- beta, IL-6, and IL-8, IL-12, TNF- alpha
Urticaria	IL-6, MMP-9, IgE-mediated immediate hypersensitivity reaction, mast cell-dependent
Seborrheic Dermatitis	CD4+/ CD8+ & TH17 cytokine release
Human Papillomavirus	TH1-cytokines, IFN- γ, downregulates IL-18, CTL responses
Vitiligo	IL-10, IL-17, IFN- γ, TNF-alpha, TH1 cytokine release, TREGs, CTL

VII. Discussion and Conclusions

The dermatoses aforementioned do share the same immunological pathways regardless of ethnicity, race, gender, and socioeconomic factors. However, the need for discovery of adequate treatment ties back to potential immunotherapies from the immunopathogeneis and cytokine profile. Treatment of allergen-related dermatoses such as atopic dermatitis and urticaria, include the use of anti-histamines. In regards to acne vulagris, TLR-2 inhibitors (isotretinoin) are used to treat severe acne due to the downregulation of TLR-2 that subsequently is upregulated with inflammatory cytokines in response to presence of *P.acnes*. Vitiligo's proposed autoimmunity has been attempted to mitigate through the use of anti-TNF-alpha inhibitors, due to the significant upregulation of TNF-alpha in this disease's pathogenesis (Alghamdi et al., 2012).

The general trend from the study reflects significantly higher rates and frequencies of skin disease in West Africa with the exception of two dermatoses. Rates of contact dermatitis are significaly higher in the United States than in West Africa while rates of the categorical viral skin dermatoses (which includes the statisticaly significant dermatosis, HPV) are significantly higher (if not the same) in the United States and in West Africa. As contact dermatitis is regularly seen through irritant and allergic contact dermatitis, it would seem as though the lack of identifiable irritants and/or allergens, to connect back to the dermatoses, frequent the West African market (Kung, Steenhoff & Gray, 2014). In regards to the only statistically significant dermatosis, HPV, rates are slightly higher in the United States. This creates speculation around the cultural comfortability of sex as a topic of discussion in Africa that may drive these lower rates of reported cases. As there is a connection of human papillomavirus to sexualy activity, there may be shame or fear of disciplinary acts upon close friends or family members (Motsomi et al., 2016).

A clear understanding of the immune profile provides way for immunomodulators to pilot the treatment and prognosis of disease. However, this immunological treatment plan needs further large-scale genome studies (Subramanian, Singh, & Jere, 2018) to understand the specific targeted genes amongst West African patients. With the current limited data and varied distribution of resources, and heterogeneity of methodology, further studies of rate of incidecne, biomedical and computational research, along with clinical treatments can truly provide fundamental and consisent treatments in West Africa, to be ethically referenced in treating the African diaspora of these same dermatoses. West Africa has been historically known to be

inconsistent with the productioin and distribution of medication and treatments leading to illness and even death (Akuse et al., 2012; Polgreen, 2009). West Africa has great potential, but does need serious assistance.

As some diseases are easily preventable and treatable, public health officials and epidemiologists can deploy messages to federal and local governing bodies. Providing affordable sunscreens while publicly supporting citizen usage can help prevent even exacerbated sequalae of most, if not all of the aforementioned dermatoses. By the year 2050, more than 50% of the United States will have skin of color (Nijhawan, Jacob, & Woolery-Lloyd, 2008). At the same time, the United States' population will be outnumbered by West Africa, specifically Nigeria, for the first time in history However, this number walks alongside the arising issues of disease are attributed to the rapid urbanization with poor infrastructure to uphold exponential growth (Aliyu & Amadu, 2017). The two occurences in the United States and West Africa reflect as a hint toward a global call-to-action to understand the skin disease that will affect a large number of the globe's population in decades to come.

References

Abraham, J., & Mathew, S. (2019). Merkel Cells: A Collective Review of Current Concepts. International journal of applied & basic medical research, 9(1), 9–13. https://doi.org/10.4103/ijabmr.IJABMR_34_18

Abulnaja K. O. (2009). Changes in the hormone and lipid profile of obese adolescent Saudi females with acne vulgaris. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas, 42(6), 501–505. https://doi.org/10.1590/s0100-879x2009000600005

Akinboro, A. O., Onayemi, O., & Mejiuni, A. D. (2013). Frequency, pattern, and extent of skin diseases in relation to CD4 cell count among adults with human immunodeficiency virus infection or acquired immunodeficiency syndrome in Osogbo, southwestern Nigeria. International Journal of Dermatology, 53(4), 416-424. doi:10.1111/j.1365-4632.2012.05820.x

Aksut, C. K., Dellavalle, R., & Naghavi, M. (2017). 181 Global skin disease morbidity and mortality: An update from the Global Burden of Disease Study 2013. Journal of Investigative Dermatology, 137(5). doi:10.1016/j.jid.2017.02.196

Akuse, R. M., Eke, F. U., Ademola, A. D., Fajolu, I. B., Gbelee, H. O., Ihejiahi, U., Bugaje, M. A., Anochie, I. C., Asinobi, A. O., Okafor, H. U., Adeleke, S. I., Audu, L. I., Otuneye, A., Disu, E., Idris, H., Aikhonbare, H., Yakubu, A., Ogala, W., Ogunrinde, O., Wammanda, R., … Awobusuyi, O. (2012). Diagnosing renal failure due to diethylene glycol in children in a resource-constrained setting. Pediatric nephrology (Berlin, Germany), 27(6), 1021–1028. https://doi.org/10.1007/s00467-011-2082-8

Alikhan, A., Felsten, L. M., Daly, M., & Petronic-Rosic, V. (2011). Vitiligo: a comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. Journal of the American Academy of Dermatology, 65(3), 473–491. https://doi.org/10.1016/j.jaad.2010.11.061

Alikhan, A., Hocker, T. L., & Chavan, R. (2017). Review of Dermatology. Edinburgh: Elsevier.

Aliyu, A. A., & Amadu, L. (2017). Urbanization, cities, and health: The challenges to Nigeria - A review. Annals of African medicine, 16(4), 149–158. https://doi.org/10.4103/aam.aam_1_17.

Amsler, E., Soria, A. & Vial-Dupuy, A. (2014). What do we learn from a cohort of 219 French patients with chronic urticaria?. Eur J Dermatol 24, 700–701. https://doi.org/10.1684/ejd.2014.2430

Agorku, E. S., Kwaansa-Ansah, E. E., Voegborlo, R. B., Amegbletor, P., & Opoku, F. (2016). Mercury and hydroquinone content of skin toning creams and cosmetic soaps, and the potential risks to the health of Ghanaian women. SpringerPlus, 5, 319. doi:10.1186/s40064-016-1967-1

Alghamdi, K. M., Khurrum, H., Taieb, A., & Ezzedine, K. (2012). Treatment of generalized vitiligo with anti-TNF-α Agents. Journal of drugs in dermatology : JDD, 11(4), 534–539.

Ashbee, H. R., Ingham, E., Holland, K. T., & Cunliffe, W. J. (1994). Cell-mediated immune responses to Malassezia furfur serovars A, B and C in patients with pityriasis versicolor, seborrheic dermatitis and controls. Experimental dermatology, 3(3), 106–112. https://doi.org/10.1111/j.1600-0625.1994.tb00267.x

Barnes K. C. (2010). An update on the genetics of atopic dermatitis: scratching the surface in 2009. The Journal of allergy and clinical immunology, 125(1), 16–31. https://doi.org/10.1016/j.jaci.2009.11.008

Bäsler, K., Bergmann, S., Heisig, M., Naegel, A., Zorn-Kruppa, M., & Brandner, J. M. (2016). The role of tight junctions in skin barrier function and dermal absorption. Journal of Controlled Release, 242, 105–118. doi: 10.1016/j.jconrel.2016.08.007

Bassiouny, D. A., & Shaker, O. (2011). Role of interleukin-17 in the pathogenesis of vitiligo. Clinical and experimental dermatology, 36(3), 292–297. https://doi.org/10.1111/j.1365-2230.2010.03972.x

Berth-Jones, J., Coulson, I., Heymann, W. R., & Lebwohl, M. (2018). Treatment of Skin Disease: Comprehensive Therapeutic Strategies. Philadelphia: Elsevier.

Berg, E. L., Yoshino, T., Rott, L. S., Robinson, M. K., Warnock, R. A., Kishimoto, T. K., Picker, L. J., & Butcher, E. C. (1991). The cutaneous lymphocyte antigen is a skin lymphocyte homing receptor for the vascular lectin endothelial cell-leukocyte adhesion molecule 1. The Journal of experimental medicine, 174(6), 1461–1466. https://doi.org/10.1084/jem.174.6.1461

Bissek, A. C., Tabah, E. N., Kouotou, E., Sini, V., Yepnjio, F. N., Nditanchou, R., … Muna, W. F. (2012). The spectrum of skin diseases in a rural setting in Cameroon (sub-Saharan Africa). BMC dermatology, 12, 7. doi:10.1186/1471-5945-12-7

Björkström, N. K., Kekäläinen, E., & Mjösberg, J. (2013). Tissue-specific effector functions of innate lymphoid cells. Immunology, 139(4), 416–427. https://doi.org/10.1111/imm.12098

Brandner, J., Zorn-Kruppa, M., Yoshida, T., Moll, I., Beck, L., & Benedetto, A. D. (2014). Epidermal tight junctions in health and disease. Tissue Barriers, 3(1-2). doi: 10.4161/21688370.2014.974451

Brinton, L. A., Figueroa, J. D., Ansong, D., Nyarko, K. M., Wiafe, S., Yarney, J., … Vanderpuye, V. (2018). Skin lighteners and hair relaxers as risk factors for breast cancer: results from the Ghana breast health study. Carcinogenesis, 39(4), 571–579. doi: 10.1093/carcin/bgy002

Brown TM, Krishnamurthy K. Histology, Dermis. [Updated 2018 Dec 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535346/

Buckland, K. (n.d.). Basophils. Retrieved from https://www.immunology.org/public-information/bitesized-immunology/cells/basophils

Bucheli, T., Strobel, B., & Hansen, H. (2018). Personal Care Products Are Only One of Many Exposure Routes of Natural Toxic Substances to Humans and the Environment. Cosmetics, 5(1), 10. doi:10.3390/cosmetics5010010

Burden of Skin Disease. (n.d.). Retrieved June 2, 2019, from https://www.aad.org/about/burden-of-skin-disease

Busam, K. J. (2010). Dermatopathology: A volume in the series Foundations in diagnostic pathology. Philadelphia: Saunders/Elsevier.

Bolognia, J., Schaffer, J. V., & Cerroni, L. (2018). Dermatology. Philadelphia: Elsevier.

Bonneville, M., O'Brien, R. L., & Born, W. K. (2010). Gammadelta T cell effector functions: a blend of innate programming and acquired plasticity. Nature reviews. Immunology, 10(7), 467–478. https://doi.org/10.1038/nri2781

Borriello, F., Granata, F., & Marone, G. (2014). Basophils and skin disorders. The Journal of investigative dermatology, 134(5), 1202–1210. https://doi.org/10.1038/jid.2014.16

Boyman O, Conrad C, Tonel G, Gilliet M, Nestle FO. (2007). The pathogenic role of tissue-resident immune cells in psoriasis. Trends Immunology, 28(2), 51-7.

Boyman O, Hefti HP, Conrad C, Nickoloff BJ, Suter M, Nestle FO. (2004). Spontaneous development of psoriasis in a new animal model shows an essential role for resident T cells and tumor necrosis factor-alpha. Journal of Experimental Medicine, 199(5). 731-6.

Braaten, K. P., & Laufer, M. R. (2008). Human Papillomavirus (HPV), HPV-Related Disease, and the HPV Vaccine. Reviews in obstetrics & gynecology, 1(1), 2–10.

Brown, D. R., Shew, M. L., Qadadri, B., Neptune, N., Vargas, M., Tu, W., Juliar, B. E., Breen, T. E., & Fortenberry, J. D. (2005). A longitudinal study of genital human papillomavirus infection in a cohort of closely followed adolescent women. The Journal of infectious diseases, 191(2), 182–192. https://doi.org/10.1086/426867

Bülbül Başkan E. (2015) Etiology and Pathogenesis of Chronic Urticaria. Turkiye Klinikleri J Dermatol-Special Topics, (8), 9–13.

Busam, K. J. (2016). Dermatopathology (A Volume in the Series Foundations in Diagnostic Pathology), Second Edition. Elsevier.

Callen, J. P., & Jorizzo, J. L. (2017). Dermatological Signs of Systemic Disease. Edinburgh: Elsevier.

Cardamone, C., Parente, R., Feo, G. D., & Triggiani, M. (2016). Mast cells as effector cells of innate immunity and regulators of adaptive immunity. Immunology Letters, 178, 10–14. doi: 10.1016/j.imlet.2016.07.003

Centers for Disease Control and Prevention. Genital HPV Infection—CDC Fact Sheet. Centers for Disease Control and Prevention. 2020.

Chambers, Emma & Vukmanovic-Stejic, Milica. (2019). Skin Barrier Immunity and Ageing. Immunology. 10.1111/imm.13152.

Chan, T. Y. (2011). Inorganic mercury poisoning associated with skin-lightening cosmetic products. Clinical Toxicology, 49(10), 886-891. doi:10.3109/15563650.2011.626425

Chen, Stella & Zhang, Ling-Juan & Gallo, Rich. (2019). Dermal White Adipose Tissue: A Newly Recognized Layer of Skin Innate Defense. Journal of Investigative Dermatology. 139. 10.1016/j.jid.2018.12.031.

Chen, Y., & Lyga, J. (2014). Brain-Skin Connection: Stress, Inflammation and Skin Aging. Inflammation & Allergy-Drug Targets, 13(3), 177-190. doi:10.2174/1871528113666140522104422

Chiricozzi, A., Romanelli, P., Volpe, E., Borsellino, G., & Romanelli, M. (2018). Scanning the Immunopathogenesis of Psoriasis. International Journal of Molecular Sciences, 19(1), 179. doi:10.3390/ijms19010179

Aktan Ş.(2015). Physical Urticarias:Pathogenesis and Diagnostic Testing Turkiye Klinikleri. J Dermatol-Special Topics, (8), 34–40.

Chow S. K. (2012). Management of chronic urticaria in Asia: 2010 AADV consensus guidelines. Asia Pacific allergy, 2(2), 149–160. https://doi.org/10.5415/apallergy.2012.2.2.149

Couteau, C., & Coiffard, L. (2016). Overview of Skin Whitening Agents: Drugs and Cosmetic Products. Cosmetics, 3(3), 27. doi:10.3390/cosmetics3030027

Conrad C, Boyman O, Tonel G, Tun-Kyi A, Laggner U, de Fougerolles A, Kotelianski V, Gardner H, Nestle FO. (2007). Alpha1beta1 integrin is crucial for accumulation of epidermal T cells and the development of psoriasis. Nature Medicine, 13(7), 836-42.

Cordain, L., Lindeberg, S., Hurtado, M., Hill, K., Eaton, S. B., & Brand-Miller, J. (2002). Acne vulgaris: a disease of Western civilization. Archives of dermatology, 138(12), 1584–1590. https://doi.org/10.1001/archderm.138.12.1584

Crawford, N. G., Kelly, D. E., Hansen, M., Beltrame, M. H., Fan, S., Bowman, S. L., … Tishkoff, S. A. (2017). Loci associated with skin pigmentation identified in African populations. Science (New York, N.Y.), 358(6365), eaan8433. doi:10.1126/science.aan8433

Cruz, M. S., Diamond, A., Russell, A., & Jameson, J. M. (2018). Human αβ and γδ T Cells in Skin Immunity and Disease. Frontiers in immunology, 9, 1304. https://doi.org/10.3389/fimmu.2018.01304

Danso, M. O., van Drongelen, V., Mulder, A., van Esch, J., Scott, H., van Smeden, J., El Ghalbzouri, A., & Bouwstra, J. A. (2014). TNF-α and Th2 cytokines induce atopic dermatitis-like features on epidermal differentiation proteins and stratum corneum lipids in human skin equivalents. The Journal of investigative dermatology, 134(7), 1941–1950. https://doi.org/10.1038/jid.2014.83

de Freitas, A. C., de Oliveira, T., Barros, M. R., Jr, & Venuti, A. (2017). hrHPV E5 oncoprotein: immune evasion and related immunotherapies. Journal of experimental & clinical cancer research : CR, 36(1), 71. https://doi.org/10.1186/s13046-017-0541-1

Debes, G. F., & Mcgettigan, S. E. (2019). Skin-Associated B Cells in Health and Inflammation. The Journal of Immunology, 202(6), 1659-1666. doi:10.4049/jimmunol.1801211

Del Rosso J. Q. (2009). Perspectives on seborrheic dermatitis: looking back to move ahead. Clinics in dermatology, 27(6 Suppl), S39–S40. https://doi.org/10.1016/j.clindermatol.2009.09.001

Di Cesare, A., Di Meglio, P., & Nestle, F. O. (2009). The IL-23/Th17 axis in the immunopathogenesis of psoriasis. The Journal of investigative dermatology, 129(6), 1339–1350. https://doi.org/10.1038/jid.2009.59

Dilek, F., Ozceker, D., Ozkaya, E., Tamay, Z., Yazici, M., Kesgin, S., Kocyigit, A., & Guler, N. (2016). Plasma Levels of Matrix Metalloproteinase-9 in Children With Chronic Spontaneous Urticaria. Allergy, asthma & immunology research, 8(6), 522–526. https://doi.org/10.4168/aair.2016.8.6.522

Dou, J., Zeng, J., Wu, K., Tan, W., Gao, L., & Lu, J. (2019). Microbiosis in pathogenesis and intervention of atopic dermatitis. International Immunopharmacology, 69, 263-269. doi:10.1016/j.intimp.2019.01.030

Dreno, B., Gollnick, H. P., Kang, S., Thiboutot, D., Bettoli, V., Torres, V., Leyden, J., & Global Alliance to Improve Outcomes in Acne (2015). Understanding innate immunity and inflammation in acne: implications for management. Journal of the European Academy of Dermatology and Venereology : JEADV, 29 Suppl 4, 3–11. https://doi.org/10.1111/jdv.13190

Dunston, G. M., & Halder, R. M. (1990). Vitiligo is associated with HLA-DR4 in black patients. A preliminary report. Archives of dermatology, 126(1), 56–60.

Dwivedi, M., Kemp, E. H., Laddha, N. C., Mansuri, M. S., Weetman, A. P., & Begum, R. (2015). Regulatory T cells in vitiligo: Implications for pathogenesis and therapeutics. Autoimmunity reviews, 14(1), 49–56. https://doi.org/10.1016/j.autrev.2014.10.002

Economic Community of West African States(ECOWAS). (n.d.). Retrieved from https://www.ecowas.int/member-states/.

Egbuniwe, I. U., Karagiannis, S. N., Nestle, F. O., & Lacy, K. E. (2015). Revisiting the role of B cells in skin immune surveillance. Trends in Immunology, 36(2), 102-111. doi:10.1016/j.it.2014.12.006

El-Khateeb, E. A., Imam, A. A., & Sallam, M. A. (2011). Pattern of skin diseases in Cairo, Egypt. International Journal of Dermatology, 50(7), 844-853. doi:10.1111/j.1365-4632.2010.04840.x

Elder, D. E., & Lever, W. F. (2015). Lever's Histopathology of the Skin. Philadelphia: Lippincott Williams & Wilkins.

Epidemiology and Management of Common Skin Diseases in ... (n.d.). Retrieved from https://apps.who.int/iris/bitstream/handle/10665/69229/WHO_FCH_CAH_05.12_eng.pdf;sequence=1

Ercis, M., Balci, S., & Atakan, N. (1996). Dermatological manifestations of 71 Down syndrome children admitted to a clinical genetics unit. Clinical genetics, 50(5), 317–320. https://doi.org/10.1111/j.1399-0004.1996.tb02381.x

Eyerich, K., Foerster, S., Rombold, S., Seidl, H. P., Behrendt, H., Hofmann, H., Ring, J., & Traidl-Hoffmann, C. (2008). Patients with chronic mucocutaneous candidiasis exhibit reduced production of Th17-associated cytokines IL-17 and IL-22. The Journal of investigative dermatology, 128(11), 2640–2645. https://doi.org/10.1038/jid.2008.139

Ezzedine, K., Lim, H. W., Suzuki, T., Katayama, I., Hamzavi, I., Lan, C. C., Goh, B. K., Anbar, T., Silva de Castro, C., Lee, A. Y., Parsad, D., van Geel, N., Le Poole, I. C., Oiso, N., Benzekri, L., Spritz, R., Gauthier, Y., Hann, S. K., Picardo, M., Taieb, A., … Vitiligo Global Issue Consensus Conference Panelists (2012). Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. Pigment cell & melanoma research, 25(3), E1–E13. https://doi.org/10.1111/j.1755-148X.2012.00997.x

Faergemann, J., Bergbrant, I. M., Dohsé, M., Scott, A., & Westgate, G. (2001). Seborrhoeic dermatitis and Pityrosporum (Malassezia) folliculitis: characterization of inflammatory cells and mediators in the skin by immunohistochemistry. The British journal of dermatology, 144(3), 549–556. https://doi.org/10.1046/j.1365-2133.2001.04082.x

Ferrante, G., Scavone, V., Muscia, M. C., Adrignola, E., Corsello, G., Passalacqua, G., & La Grutta, S. (2015). The care pathway for children with urticaria, angioedema, mastocytosis. The World Allergy Organization journal, 8(1), 5. https://doi.org/10.1186/s40413-014-0052-x

Ferrer, M., Nakazawa, K., & Kaplan, A. P. (1999). Complement dependence of histamine release in chronic urticaria. The Journal of allergy and clinical immunology, 104(1), 169–172. https://doi.org/10.1016/s0091-6749(99)70129-6

Fuller, B. (2019). Role of PGE-2 and Other Inflammatory Mediators in Skin Aging and Their Inhibition by Topical Natural Anti-Inflammatories. Cosmetics, 6(1), 6. doi:10.3390/cosmetics6010006

Foster-Powell, K., Holt, S. H., & Brand-Miller, J. C. (2002). International table of glycemic index and glycemic load values: 2002. The American journal of clinical nutrition, 76(1), 5–56. https://doi.org/10.1093/ajcn/76.1.5

Fitz-Gibbon, S., Tomida, S., Chiu, B. H., Nguyen, L., Du, C., Liu, M., Elashoff, D., Erfe, M. C., Loncaric, A., Kim, J., Modlin, R. L., Miller, J. F., Sodergren, E., Craft, N., Weinstock, G. M., & Li, H. (2013). Propionibacterium acnes strain populations in the human skin microbiome associated with acne. The Journal of investigative dermatology, 133(9), 2152–2160. https://doi.org/10.1038/jid.2013.21

Gaitanis, G., Magiatis, P., Stathopoulou, K., Bassukas, I. D., Alexopoulos, E. C., Velegraki, A., & Skaltsounis, A. L. (2008). AhR ligands, malassezin, and indolo[3,2-b]carbazole are selectively produced by Malassezia furfur strains isolated from seborrheic dermatitis. The Journal of investigative dermatology, 128(7), 1620–1625. https://doi.org/10.1038/sj.jid.5701252

Gallucci, R. M., Sloan, D. K., Heck, J. M., Murray, A. R., & Odell, S. J. (2004). Interleukin 6 Indirectly Induces Keratinocyte Migration. Journal of Investigative Dermatology, 122(3), 764–772. doi: 10.1111/j.0022-202x.2004.22323.x

Galluzzi, L., Vacchelli, E., Eggermont, A., Fridman, W. H., Galon, J., Sautès-Fridman, C., Tartour, E., Zitvogel, L., & Kroemer, G. (2012). Trial Watch: Experimental Toll-like receptor agonists for cancer therapy. Oncoimmunology, 1(5), 699–716. https://doi.org/10.4161/onci.20696

Gebhardt T., Wakim L.M., Eidsmo L., Reading P.C., Heath W.R., Carbone F.R. (2009). Memory T cells in nonlymphoid tissue that provide enhanced local immunity during infection with herpes simplex virus. Nature Immunology, 10(5), 524-30.

Gerber J.S., Mosser D.M. (2001). Reversing lipopolysaccharide toxicity by ligating the macrophage Fcγ receptors. Journal of Immunology, 166(11), 6861–6868. doi:10.4049/jimmunol.166.11.6861

GHO | By category | Population - Data by WHO region. (n.d.). Retrieved from https://apps.who.int/gho/data/view.main.POP2020

Gokhale, B. B., & Mehta, L. N. (1983). Histopathology of vitiliginous skin. International journal of dermatology, 22(8), 477–480. https://doi.org/10.1111/j.1365-4362.1983.tb02178.x

Gohara, M. (2015). Skin cancer: An African perspective. British Journal of Dermatology, 173, 17-21. doi:10.1111/bjd.13380

Grabowska, A. K., & Riemer, A. B. (2012). The invisible enemy - how human papillomaviruses avoid recognition and clearance by the host immune system. The open virology journal, 6, 249–256. https://doi.org/10.2174/1874357901206010249

Gregorio, J., Meller, S., Conrad, C., Di Nardo, A., Homey, B., Lauerma, A., Arai, N., Gallo, R. L., Digiovanni, J., & Gilliet, M. (2010). Plasmacytoid dendritic cells sense skin injury and promote wound healing through type I interferons. The Journal of experimental medicine, 207(13), 2921–2930. https://doi.org/10.1084/jem.20101102

Guiducci, C., Tripodo, C., Gong, M., Sangaletti, S., Colombo, M. P., Coffman, R. L., & Barrat, F. J. (2010). Autoimmune skin inflammation is dependent on plasmacytoid dendritic cell activation by nucleic acids via TLR7 and TLR9. The Journal of experimental medicine, 207(13), 2931–2942. https://doi.org/10.1084/jem.20101048

Guilliams, M., Ginhoux, F., Jakubzick, C. et al.(2014) Dendritic cells, monocytes and macrophages: a unified nomenclature based on ontogeny. Nat Rev Immunol 14, 571–578. https://doi.org/10.1038/nri3712

Gupta, A. K., & Bluhm, R. (2004). Seborrheic dermatitis. Journal of the European Academy of Dermatology and Venereology : JEADV, 18(1), 13–20. https://doi.org/10.1111/j.1468-3083.2004.00693.x

Goh, C. L., & Akarapanth, R. (1994). Epidemiology of skin disease among children in a referral skin clinic in Singapore. Pediatric dermatology, 11(2), 125–128. https://doi.org/10.1111/j.1525-1470.1994.tb00565.x

Habif, T. P. (2016). Clinical Dermatology: A Color Guide to Diagnosis and Therapy. St. Louis, MO: Elsevier

Haniffa, M. A., Wang, X.-N., Holtick, U., Rae, M., Isaacs, J. D., Dickinson, A. M., … Collin, M. P. (2007). Adult Human Fibroblasts Are Potent Immunoregulatory Cells and Functionally Equivalent to Mesenchymal Stem Cells. The Journal of Immunology, 179(3), 1595–1604. doi: 10.4049/jimmunol.179.3.1595

Havran WL, Chien YH, Allison JP. Recognition of self antigens by skin-derived T cells with invariant gamma delta antigen receptors. Science. 1991;252(5011):1430-1432. doi:10.1126/science.1828619

Hay, R. J., Johns, N. E., Williams, H. C., Bolliger, I. W., Dellavalle, R. P., Margolis, D. J., . . . Naghavi, M. (2014). The Global Burden of Skin Disease in 2010: An Analysis of the Prevalence and Impact of Skin Conditions. Journal of Investigative Dermatology, 134(6), 1527-1534. doi:10.1038/jid.2013.446

Hay, R.; Steer, A.; Engelman, D.; Walton, S. Scabies in the developing world—Its prevalence, complications, and management. Clin. Microbiol. Infect. 2012, 18, 313–323.

Hees, C. V., & Naafs, B. (2009). Common skin diseases in Africa: An illustrated guide. Voorburg: Stichting TrodermaVan Hees.

Henshaw, Eshan & Ibekwe, Perpetua & Adeyemi, Adedayo & Ameh, Soter & Ogedegbe, Evelyn & Archibong, Joseph & Olasode, Olayinka. (2018). Dermatologic Practice Review of Common Skin Diseases in Nigeria. International Journal of Health Sciences and Research. 8. 235-248.

Hoeffel, G., Wang, Y., Greter, M., See, P., Teo, P., Malleret, B., … Ginhoux, F. (2012). Adult Langerhans cells derive predominantly from embryonic fetal liver monocytes with a minor contribution of yolk sac-derived macrophages. The Journal of experimental medicine, 209(6), 1167–1181. doi:10.1084/jem.20120340

Hogewoning, C. J., Bleeker, M. C., van den Brule, A. J., Voorhorst, F. J., Snijders, P. J., Berkhof, J., Westenend, P. J., & Meijer, C. J. (2003). Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial. International journal of cancer, 107(5), 811–816. https://doi.org/10.1002/ijc.11474

Hollestein, L. M., & Nijsten, T. (2014). An Insight into the Global Burden of Skin Diseases. Journal of Investigative Dermatology, 134(6), 1499-1501. doi:10.1038/jid.2013.513

Howell, M. D., Fairchild, H. R., Kim, B. E., Bin, L., Boguniewicz, M., Redzic, J. S., Hansen, K. C., & Leung, D. Y. (2008). Th2 cytokines act on S100/A11 to downregulate keratinocyte differentiation. The Journal of investigative dermatology, 128(9), 2248–2258. https://doi.org/10.1038/jid.2008.74

Howitz, J., Brodthagen, H., Schwartz, M., & Thomsen, K. (1977). Prevalence of vitiligo. Epidemiological survey on the Isle of Bornholm, Denmark. Archives of dermatology, 113(1), 47–52. https://doi.org/10.1001/archderm.113.1.47

Iannella, G., Greco, A., Didona, D., Didona, B., Granata, G., Manno, A., Pasquariello, B., & Magliulo, G. (2016). Vitiligo: Pathogenesis, clinical variants and treatment approaches. Autoimmunity reviews, 15(4), 335–343. https://doi.org/10.1016/j.autrev.2015.12.006

Igawa, S., & Nardo, A. D. (2017). Skin microbiome and mast cells. Translational Research, 184, 68–76. doi: 10.1016/j.trsl.2017.03.003

Ingham, E., Eady, E. A., Goodwin, C. E., Cove, J. H., & Cunliffe, W. J. (1992). Pro-inflammatory levels of interleukin-1 alpha-like bioactivity are present in the majority of open comedones in acne vulgaris. The Journal of investigative dermatology, 98(6), 895–901. https://doi.org/10.1111/1523-1747.ep12460324

Ismail, N. H., Manaf, Z. A., & Azizan, N. Z. (2012). High glycemic load diet, milk and ice cream consumption are related to acne vulgaris in Malaysian young adults: a case control study. BMC dermatology, 12, 13. https://doi.org/10.1186/1471-5945-12-13

Iwegbue, C., Bassey, F. I., Obi, G., Tesi, G. O., & Martincigh, B. S. (2016). Concentrations and exposure risks of some metals in facial cosmetics in Nigeria. Toxicology reports, 3, 464–472. doi:10.1016/j.toxrep.2016.04.004

Iwegbue, C., Emakunu, O. S., Obi, G., Nwajei, G. E., & Martincigh, B. S. (2016). Evaluation of human exposure to metals from some commonly used hair care products in Nigeria. Toxicology reports, 3, 796–803. doi:10.1016/j.toxrep.2016.10.001

Jacquemin, C., Rambert, J., Guillet, S., Thiolat, D., Boukhedouni, N., Doutre, M. S., … Seneschal, J. (2017). Heat shock protein 70 potentiates interferon alpha production by plasmacytoid dendritic cells: relevance for cutaneous lupus and vitiligo pathogenesis. British Journal of Dermatology, 177(5), 1367–1375. doi: 10.1111/bjd.15550

James, W. D., Elston, D. M., & McMahon, P. J. (2018). Andrews' Diseases of the Skin Clinical Atlas. Edinburgh: Elsevier.

Jin, Y., Mailloux, C. M., Gowan, K., Riccardi, S. L., LaBerge, G., Bennett, D. C., Fain, P. R., & Spritz, R. A. (2007). NALP1 in vitiligo-associated multiple autoimmune disease. The New England journal of medicine, 356(12), 1216–1225. https://doi.org/10.1056/NEJMoa061592

Johns, N. E., Hay, R. J., Wulf, S., & Naghavi, M. (2013). A systematic analysis of the global burden of skin disease: Lesions learned. The Lancet, 381. doi:10.1016/s0140-6736(13)61321-5

Johnson MT, Roberts J. Skin conditions and related need for medical care among persons 1–74 years. United States, 1971– 1974. Vital Health Stat 11 1978; 212:i–v, 1–72

Kagotho, E., Omuse, G., Okinda, N., & Ojwang, P. (2018). Vitamin D status in healthy black African adults at a tertiary hospital in Nairobi, Kenya: a cross sectional study. BMC endocrine disorders, 18(1), 70. https://doi.org/10.1186/s12902-018-0296-5

Kang, S., Amagai, M., Bruckner, A. L., Erik, A. H., Margolis, D. J., McMichael, A. J., & Orringer, J. S. (2019). Fitzpatrick's dermatology (9th ed., Vol. 1). New York, New York: McGraw-Hill Education.

Kanitakis, J., Morelon, E., Petruzzo, P., Badet, L., & Dubernard, J.-M. (2010). Self-renewal capacity of human epidermal Langerhans cells: observations made on a composite tissue

allograft. Experimental Dermatology, 20(2), 145–146. doi: 10.1111/j.1600-0625.2010.01146.x

Karimkhani, C., Dellavalle, R. P., Coffeng, L. E., Flohr, C., Hay, R. J., Langan, S. M., Nsoesie, E. O., Ferrari, A. J., Erskine, H. E., Silverberg, J. I., Vos, T., & Naghavi, M. (2017). Global Skin Disease Morbidity and Mortality: An Update From the Global Burden of Disease Study 2013. JAMA dermatology, 153(5), 406–412. https://doi.org/10.1001/jamadermatol.2016.5538

Kartono, F., & Maibach, H. I. (2006). Irritants in combination with a synergistic or additive effect on the skin response: an overview of tandem irritation studies. Contact dermatitis, 54(6), 303–312. https://doi.org/10.1111/j.0105-1873.2006.00792.x

Kashem SW, Haniffa M, Kaplan DH. Antigen-presenting cells in the skin. Annu Rev Immunol. 2017;35:469–499. doi:10.1146/annurev-immunol-051116-052215 [PubMed] [CrossRef] [Google Scholar]

Kasperska-Zajac, A., Grzanka, A., & Damasiewicz-Bodzek, A. (2015). IL-6 Transsignaling in Patients with Chronic Spontaneous Urticaria. PloS one, 10(12), e0145751. https://doi.org/10.1371/journal.pone.0145751

Katsarou, A., & Armenaka, M. (2011). Atopic dermatitis in older patients: particular points. Journal of the European Academy of Dermatology and Venereology : JEADV, 25(1), 12–18. https://doi.org/10.1111/j.1468-3083.2010.03737.x

Kawamura, T., Ogawa, Y., Aoki, R., & Shimada, S. (2014). Innate and intrinsic antiviral immunity in skin. Journal of Dermatological Science, 75(3), 159–166. doi: 10.1016/j.jdermsci.2014.05.004

Kayiran, M. A., & Akdeniz, N. (2019). Diagnosis and treatment of urticaria in primary care. Northern clinics of Istanbul, 6(1), 93–99. https://doi.org/10.14744/nci.2018.75010

Kaymak Y, Adisen E, Ilter N et al. Dietary glycemic index and glucose, insulin, insulin-like growth factor-I, insulin-like growth factor binding protein 3, and leptin levels in patients with acne. J Am Acad Dermatol 2007; 57:819–23.

Kelhälä, H. L., Palatsi, R., Fyhrquist, N., Lehtimäki, S., Väyrynen, J. P., Kallioinen, M., Kubin, M. E., Greco, D., Tasanen, K., Alenius, H., Bertino, B., Carlavan, I., Mehul, B., Déret, S., Reiniche, P., Martel, P., Marty, C., Blume-Peytavi, U., Voegel, J. J., & Lauerma, A. (2014). IL-17/Th17 pathway is activated in acne lesions. PloS one, 9(8), e105238. https://doi.org/10.1371/journal.pone.0105238

Kelly, A. P., Taylor, S. C., Lim, H. W., & Maria, A. S. (2016). Taylor and Kelly's Dermatology for Skin of Color. New York, NY: McGraw-Hill Education.

Kemp, E. H., Emhemad, S., Akhtar, S., Watson, P. F., Gawkrodger, D. J., & Weetman, A. P. (2011). Autoantibodies against tyrosine hydroxylase in patients with non-segmental

(generalised) vitiligo. Experimental dermatology, 20(1), 35–40. https://doi.org/10.1111/j.1600-0625.2010.01181.x

Kesavan, S., Holland, K. T., & Ingham, E. (2000). The effects of lipid extraction on the immunomodulatory activity of Malassezia species in vitro. Medical mycology, 38(3), 239–247. https://doi.org/10.1080/mmy.38.3.239.247

Kieffer, M., Bergbrant, I. M., Faergemann, J., Jemec, G. B., Ottevanger, V., Stahl Skov, P., & Svejgaard, E. (1990). Immune reactions to Pityrosporum ovale in adult patients with atopic and seborrheic dermatitis. Journal of the American Academy of Dermatology, 22(5 Pt 1), 739–742. https://doi.org/10.1016/0190-9622(90)70100-v

Kim, J. E., Kim, J. S., Cho, D. H., & Park, H. J. (2016). Molecular Mechanisms of Cutaneous Inflammatory Disorder: Atopic Dermatitis. International journal of molecular sciences, 17(8), 1234. https://doi.org/10.3390/ijms17081234

Kim, J., Ochoa, M. T., Krutzik, S. R., Takeuchi, O., Uematsu, S., Legaspi, A. J., Brightbill, H. D., Holland, D., Cunliffe, W. J., Akira, S., Sieling, P. A., Godowski, P. J., & Modlin, R. L. (2002). Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. Journal of immunology (Baltimore, Md. : 1950), 169(3), 1535–1541. https://doi.org/10.4049/jimmunol.169.3.1535

Kim, B. S., Wojno, E. D., & Artis, D. (2013). Innate lymphoid cells and allergic inflammation. Current opinion in immunology, 25(6), 738–744. doi:10.1016/j.coi.2013.07.013

Kjaer, H. F., Eller, E., Høst, A., Andersen, K. E., & Bindslev-Jensen, C. (2008). The prevalence of allergic diseases in an unselected group of 6-year-old children. The DARC birth cohort study. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology, 19(8), 737–745. https://doi.org/10.1111/j.1399-3038.2008.00733.x

Klicznik, M., Szenes-Nagy, A., Campbell, D., & Gratz, I. (2018). Taking the lead – how keratinocytes orchestrate skin T cell immunity. Immunology Letters, 200, 43–51. doi: 10.1016/j.imlet.2018.06.009

Klonowska, J., Gleń, J., Nowicki, R., & Trzeciak, M. (2018). New Cytokines in the Pathogenesis of Atopic Dermatitis—New Therapeutic Targets. International Journal of Molecular Sciences, 19(10), 3086. doi:10.3390/ijms19103086

Knipper, J. A., Willenborg, S., Brinckmann, J., Bloch, W., Maaß, T., Wagener, R., Krieg, T., Sutherland, T., Munitz, A., Rothenberg, M. E., Niehoff, A., Richardson, R., Hammerschmidt, M., Allen, J. E., & Eming, S. A. (2015). Interleukin-4 Receptor α Signaling in Myeloid Cells Controls Collagen Fibril Assembly in Skin Repair. Immunity, 43(4), 803–816. https://doi.org/10.1016/j.immuni.2015.09.005

Kollisch, G., Kalali, B. N., Voelcker, V., Wallich, R., Behrendt, H., Ring, J., … Ollert, M. (2005). Various members of the Toll-like receptor family contribute to the innate immune

response of human epidermal keratinocytes. Immunology, 114(4), 531–541. doi: 10.1111/j.1365-2567.2005.02122.x

Koutsky L. (1997). Epidemiology of genital human papillomavirus infection. The American journal of medicine, 102(5A), 3–8. https://doi.org/10.1016/s0002-9343(97)00177-0

Kulthanan, K., Chiawsirikajorn, Y., & Jiamton, S. (2008). Acute urticaria: etiologies, clinical course and quality of life. Asian Pacific journal of allergy and immunology, 26(1), 1–9.

Kung, S. J., Steenhoff, A. P., & Gray, C. (2014). Food allergy in Africa: myth or reality?. Clinical reviews in allergy & immunology, 46(3), 241–249. https://doi.org/10.1007/s12016-012-8341-z

Kwiecien, K., Zegar, A., Jung, J., Brzoza, P., Kwitniewski, M., Godlewska, U., Grygier, B., Kwiecinska, P., Morytko, A., & Cichy, J. (2019). Architecture of antimicrobial skin defense. Cytokine & growth factor reviews, 49, 70–84. https://doi.org/10.1016/j.cytogfr.2019.08.001

LaBerge, G. S., Bennett, D. C., Fain, P. R., & Spritz, R. A. (2008). PTPN22 is genetically associated with risk of generalized vitiligo, but CTLA4 is not. The Journal of investigative dermatology, 128(7), 1757–1762. https://doi.org/10.1038/sj.jid.5701233

Lally, A., Casabonne, D., Newton, R., & Wojnarowska, F. (2010). Seborrheic dermatitis among Oxford renal transplant recipients. Journal of the European Academy of Dermatology and Venereology : JEADV, 24(5), 561–564. https://doi.org/10.1111/j.1468-3083.2009.03470.x

Landriscina, A., Rosen, J., & Friedman, A. (2015). Nanotechnology, Inflammation and the Skin Barrier: Innovative Approaches for Skin Health and Cosmesis. Cosmetics, 2(2), 177-186. doi:10.3390/cosmetics2020177

Lang, K. S., Caroli, C. C., Muhm, A., Wernet, D., Moris, A., Schittek, B., Knauss-Scherwitz, E., Stevanovic, S., Rammensee, H. G., & Garbe, C. (2001). HLA-A2 restricted, melanocyte-specific CD8(+) T lymphocytes detected in vitiligo patients are related to disease activity and are predominantly directed against MelanA/MART1. The Journal of investigative dermatology, 116(6), 891–897. https://doi.org/10.1046/j.1523-1747.2001.01363.x

Lapi, F., Cassano, N., Pegoraro, V., Cataldo, N., Heiman, F., Cricelli, I., Levi, M., Colombo, D., Zagni, E., Cricelli, C., & Vena, G. A. (2016). Epidemiology of chronic spontaneous urticaria: results from a nationwide, population-based study in Italy. The British journal of dermatology, 174(5), 996–1004. https://doi.org/10.1111/bjd.14470

Larouche, J., Sheoran, S., Maruyama, K., & Martino, M. M. (2018). Immune Regulation of Skin Wound Healing: Mechanisms and Novel Therapeutic Targets. Advances in Wound Care, 7(7), 209–231. doi: 10.1089/wound.2017.0761

Law, M. P., Chuh, A. A., Lee, A., & Molinari, N. (2010). Acne prevalence and beyond: acne disability and its predictive factors among Chinese late adolescents in Hong

Kong. Clinical and experimental dermatology, 35(1), 16–21. https://doi.org/10.1111/j.1365-2230.2009.03340.x

Lee, H. J., Jeong, S. E., Lee, S., Kim, S., Han, H., & Jeon, C. O. (2017). Effects of cosmetics on the skin microbiome of facial cheeks with different hydration levels. MicrobiologyOpen, 7(2), e00557. doi:10.1002/mbo3.557

Lee, H. Y., Stieger, M., Yawalkar, N., & Kakeda, M. (2013). Cytokines and chemokines in irritant contact dermatitis. Mediators of inflammation, 2013, 916497. https://doi.org/10.1155/2013/916497

Lephart, E. (2018). Equol's Anti-Aging Effects Protect against Environmental Assaults by Increasing Skin Antioxidant Defense and ECM Proteins While Decreasing Oxidative Stress and Inflammation. Cosmetics, 5(1), 16. doi:10.3390/cosmetics501001

Le Poole, I. C., Das, P. K., van den Wijngaard, R. M., Bos, J. D., & Westerhof, W. (1993). Review of the etiopathomechanism of vitiligo: a convergence theory. Experimental dermatology, 2(4), 145–153. https://doi.org/10.1111/j.1600-0625.1993.tb00023.x

Levin, C., Bonduelle, O., Nuttens, C., Primard, C., Verrier, B., Boissonnas, A., & Combadière, B. (2017). Critical Role for Skin-Derived Migratory DCs and Langerhans Cells in TFH and GC Responses after Intradermal Immunization. Journal of Investigative Dermatology, 137(9), 1905–1913. doi: 10.1016/j.jid.2017.04.016

Lim, H. W., Collins, S. A., Resneck, J. S., Bolognia, J. L., Hodge, J. A., Rohrer, T. A., . . . Moyano, J. V. (2017). The burden of skin disease in the United States. Journal of the American Academy of Dermatology, 76(5). doi:10.1016/j.jaad.2016.12.043

Linhart, C., Talasz, H., Morandi, E. M., Exley, C., Lindner, H. H., Taucher, S., … Ulmer, H. (2017). Use of Underarm Cosmetic Products in Relation to Risk of Breast Cancer: A Case-Control Study. EBioMedicine, 21, 79–85. doi:10.1016/j.ebiom.2017.06.005

Litchman, G., Nair, P. A., Atwater, A. R., & Bhutta, B. S. (2020). Contact Dermatitis. In StatPearls. StatPearls Publishing.

Long, H., Zhang, G., Wang, L., & Lu, Q. (2015). Eosinophilic Skin Diseases: A Comprehensive Review. Clinical Reviews in Allergy & Immunology,50(2), 189-213. doi:10.1007/s12016-015-8485-8

Lu, Q., Chang, C. C., & Richardson, B. C. (2015). Epigenetics and dermatology. Amsterdam: Elsevier/AP, Academic Press is an imprint of Elsevier.

Lucas, T., Waisman, A., Ranjan, R., Roes, J., Krieg, T., Müller, W., … Eming, S. A. (2010). Differential Roles of Macrophages in Diverse Phases of Skin Repair. The Journal of Immunology, 184(7), 3964–3977. doi: 10.4049/jimmunol.0903356

Lucky, A. W., Biro, F. M., Simbartl, L. A., Morrison, J. A., & Sorg, N. W. (1997). Predictors of severity of acne vulgaris in young adolescent girls: results of a five-year longitudinal study. The Journal of pediatrics, 130(1), 30–39. https://doi.org/10.1016/s0022-3476(97)70307-x

Macdonald R. (2005). Access to clean water in rural Africa is inadequate. BMJ (Clinical research ed.), 331(7508), 70. https://doi.org/10.1136/bmj.331.7508.70-h

Mak, A., & Tay, S. (2014). Environmental Factors, Toxicants and Systemic Lupus Erythematosus. International Journal of Molecular Sciences, 15(9), 16043-16056. doi:10.3390/ijms150916043

Manhart, L. E., & Koutsky, L. A. (2002). Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. Sexually transmitted diseases, 29(11), 725–735. https://doi.org/10.1097/00007435-200211000-00018

Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol. 2004;25(12):677–686. doi:10.1016/j.it.2004.09.015

Marrazzo, J. M., Koutsky, L. A., Kiviat, N. B., Kuypers, J. M., & Stine, K. (2001). Papanicolaou test screening and prevalence of genital human papillomavirus among women who have sex with women. American journal of public health, 91(6), 947–952. https://doi.org/10.2105/ajph.91.6.947

Marshall, A. S., Silva, J. R., Bannerman, C. A., Gilron, I., & Ghasemlou, N. (2019). Skin-Resident γδ T Cells Exhibit Site-Specific Morphology and Activation States. Journal of immunology research, 2019, 9020234. https://doi.org/10.1155/2019/9020234

McLaughlin, J., Watterson, S., Layton, A. M., Bjourson, A. J., Barnard, E., & McDowell, A. (2019). Propionibacterium acnes and Acne Vulgaris: New Insights from the Integration of Population Genetic, Multi-Omic, Biochemical and Host-Microbe Studies. Microorganisms, 7(5), 128. https://doi.org/10.3390/microorganisms7050128

Meylan, P., Lang, C., Mermoud, S., Johannsen, A., Norrenberg, S., Hohl, D., Vial, Y., Prod'hom, G., Greub, G., Kypriotou, M., & Christen-Zaech, S. (2017). Skin Colonization by Staphylococcus aureus Precedes the Clinical Diagnosis of Atopic Dermatitis in Infancy. The Journal of investigative dermatology, 137(12), 2497–2504. https://doi.org/10.1016/j.jid.2017.07.834

Minutti, C. M., Knipper, J. A., Allen, J. E., & Zaiss, D. M. (2017). Tissue-specific contribution of macrophages to wound healing. Seminars in Cell & Developmental Biology, 61, 3–11. doi: 10.1016/j.semcdb.2016.08.006

Mistry, N. (2017). Guidelines for Formulating Anti-Pollution Products. Cosmetics, 4(4), 57. doi:10.3390/cosmetics4040057

Miteva, M. I. (2018). A notebook of dermatopathology: Mastering the basics, pattern recognition, and key pathologic findings. Boca Raton, FL: CRC Press.

Moellmann, G., Klein-Angerer, S., Scollay, D. A., Nordlund, J. J., & Lerner, A. B. (1982). Extracellular granular material and degeneration of keratinocytes in the normally pigmented epidermis of patients with vitiligo. The Journal of investigative dermatology, 79(5), 321–330. https://doi.org/10.1111/1523-1747.ep12500086

Mohammed, T., Mohammed, E., & Bascombe, S. (2017). The evaluation of total mercury and arsenic in skin bleaching creams commonly used in Trinidad and Tobago and their potential risk to the people of the Caribbean. Journal of public health research, 6(3), 1097. doi:10.4081/jphr.2017.1097

Motsomi, K., Makanjee, C., Basera, T., & Nyasulu, P. (2016). Factors affecting effective communication about sexual and reproductive health issues between parents and adolescents in zandspruit informal settlement, Johannesburg, South Africa. The Pan African medical journal, 25, 120. https://doi.org/10.11604/pamj.2016.25.120.9208

Muñoz, N., Bosch, F. X., de Sanjosé, S., Herrero, R., Castellsagué, X., Shah, K. V., Snijders, P. J., Meijer, C. J., & International Agency for Research on Cancer Multicenter Cervical Cancer Study Group (2003). Epidemiologic classification of human papillomavirus types associated with cervical cancer. The New England journal of medicine, 348(6), 518–527. https://doi.org/10.1056/NEJMoa021641

Nelson, A., & Schneider, A. (2016). Faculty Opinions recommendation of Different Propionibacterium acnes Phylotypes Induce Distinct Immune Responses and Express Unique Surface and Secreted Proteomes. Faculty Opinions – Post-Publication Peer Review of the Biomedical Literature. doi:10.3410/f.726484083.793523707

Nestle, F. O., Di Meglio, P., Qin, J. Z., & Nickoloff, B. J. (2009). Skin immune sentinels in health and disease. Nature reviews. Immunology, 9(10), 679–691. https://doi.org/10.1038/nri2622

Nijhawan, R. I., Jacob, S. E., & Woolery-Lloyd, H. (2008). Skin of color education in dermatology residency programs: does residency training reflect the changing demographics of the United States?. Journal of the American Academy of Dermatology, 59(4), 615–618. https://doi.org/10.1016/j.jaad.2008.06.024

Njoo, M. D., & Westerhof, W. (2001). Vitiligo. Pathogenesis and treatment. American journal of clinical dermatology, 2(3), 167–181. https://doi.org/10.2165/00128071-200102030-00006

Nkansah, M. A., Opoku, F., Ephraim, J. H., Wemegah, D. D., & Tetteh, L. P. (2016). Characterization of Beauty Salon Wastewater from Kwame Nkrumah University of Science and Technology, Kumasi, Ghana, and Its Surrounding Communities. Environmental health insights, 10, 147–154. doi:10.4137/EHI.S40360

Noda, S., Krueger, J. G., & Guttman-Yassky, E. (2015). The translational revolution and use of biologics in patients with inflammatory skin diseases. The Journal of allergy and clinical immunology, 135(2), 324–336. https://doi.org/10.1016/j.jaci.2014.11.015

Nograles, K. E., Zaba, L. C., Shemer, A., Fuentes-Duculan, J., Cardinale, I., Kikuchi, T., Ramon, M., Bergman, R., Krueger, J. G., & Guttman-Yassky, E. (2009). IL-22-producing "T22" T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. The Journal of allergy and clinical immunology, 123(6), 1244–52.e2. https://doi.org/10.1016/j.jaci.2009.03.041

Norat, T., Dossus, L., Rinaldi, S., Overvad, K., Grønbaek, H., Tjønneland, A., Olsen, A., Clavel-Chapelon, F., Boutron-Ruault, M. C., Boeing, H., Lahmann, P. H., Linseisen, J., Nagel, G., Trichopoulou, A., Trichopoulos, D., Kalapothaki, V., Sieri, S., Palli, D., Panico, S., Tumino, R., … Kaaks, R. (2007). Diet, serum insulin-like growth factor-I and IGF-binding protein-3 in European women. European journal of clinical nutrition, 61(1), 91–98. https://doi.org/10.1038/sj.ejcn.1602494

Odhiambo, J. A., Williams, H. C., Clayton, T. O., Robertson, C. F., Asher, M. I., & ISAAC Phase Three Study Group (2009). Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. The Journal of allergy and clinical immunology, 124(6), 1251–8.e23. https://doi.org/10.1016/j.jaci.2009.10.009

Oladele, R. O., Toriello, C., Ogunsola, F. T., Ayanlowo, O. O., Foden, P., Fayemiwo, A. S., . . . Denning, D. W. (2018). Prior subclinical histoplasmosis revealed in Nigeria using histoplasmin skin testing. Plos One, 13(5). doi:10.1371/journal.pone.0196224

Orisakwe, O. E., & Otaraku, J. O. (2013). Metal Concentrations in Cosmetics Commonly Used in Nigeria. The Scientific World Journal, 2013, 1-7. doi:10.1155/2013/959637

Oyarbide-Valencia, K., van den Boorn, J. G., Denman, C. J., Li, M., Carlson, J. M., Hernandez, C., Nishimura, M. I., Das, P. K., Luiten, R. M., & Le Poole, I. C. (2006). Therapeutic implications of autoimmune vitiligo T cells. Autoimmunity reviews, 5(7), 486–492. https://doi.org/10.1016/j.autrev.2006.03.012

Oyedemi, B. O., Oyedemi, S. O., Chibuzor, J. V., Ijeh, I. I., Coopoosamy, R. M., & Aiyegoro, A. O. (2018). Pharmacological Evaluation of Selected Medicinal Plants Used in the Management of Oral and Skin Infections in Ebem-Ohafia District, Abia State, Nigeria. TheScientificWorldJournal, 2018, 4757458. doi:10.1155/2018/4757458

Palamaras, I., Kyriakis, K. P., & Stavrianeas, N. G. (2012). Seborrheic dermatitis: lifetime detection rates. Journal of the European Academy of Dermatology and Venereology : JEADV, 26(4), 524–526. https://doi.org/10.1111/j.1468-3083.2011.04079.x

Palmer, C., Irvine, A., Terron-Kwiatkowski, A. et al. (2006). Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nature Genetics 38, 441–446 . https://doi.org/10.1038/ng1767

Palermo, B., Campanelli, R., Garbelli, S., Mantovani, S., Lantelme, E., Brazzelli, V., Ardigó, M., Borroni, G., Martinetti, M., Badulli, C., Necker, A., & Giachino, C. (2001). Specific cytotoxic T lymphocyte responses against Melan-A/MART1, tyrosinase and gp100 in vitiligo by the use of major histocompatibility complex/peptide tetramers: the role of cellular immunity in the etiopathogenesis of vitiligo. The Journal of investigative dermatology, 117(2), 326–332. https://doi.org/10.1046/j.1523-1747.2001.01408.x

Patterson, J. W., Hosler, G. A., & Weedon, D. (2016). Weedon's Skin Pathology. Edinburgh: Elsevier Churchill Lvgst.

Pickart, L., Vasquez-Soltero, J., & Margolina, A. (2015). GHK-Cu may Prevent Oxidative Stress in Skin by Regulating Copper and Modifying Expression of Numerous Antioxidant Genes. Cosmetics, 2(3), 236-247. doi:10.3390/cosmetics2030236

Poisoned teething drug arrests. Sky News. Feb 11, 2009.

Prohic A. (2010). Distribution of Malassezia species in seborrhoeic dermatitis: correlation with patients' cellular immune status. Mycoses, 53(4), 344–349. https://doi.org/10.1111/j.1439-0507.2009.01713.x

Proksch, E., Brandner, J. M., & Jensen, J.-M. (2008). The skin: an indispensable barrier. Experimental Dermatology, 17(12), 1063–1072. doi: 10.1111/j.1600-0625.2008.00786.x

Qiu, F., Maniar, A., Diaz, M. Q., Chapoval, A. I., & Medvedev, A. E. (2010). Activation of cytokine-producing and antitumor activities of natural killer cells and macrophages by engagement of Toll-like and NOD-like receptors. Innate Immunity, 17(4), 375–387. doi: 10.1177/1753425910372000

Rajan, J. P., Simon, R. A., & Bosso, J. V. (2014). Prevalence of sensitivity to food and drug additives in patients with chronic idiopathic urticaria. The journal of allergy and clinical immunology. In practice, 2(2), 168–171. https://doi.org/10.1016/j.jaip.2013.10.002

Ratzinger, G., Stoitzner, P., Ebner, S., Lutz, M. B., Layton, G. T., Rainer, C., … Romani, N. (2002). Matrix Metalloproteinases 9 and 2 Are Necessary for the Migration of Langerhans Cells and Dermal Dendritic Cells from Human and Murine Skin. The Journal of Immunology, 168(9), 4361–4371. doi: 10.4049/jimmunol.168.9.4361

Rea, J. N., Newhouse, M. L., & Halil, T. (1976). Skin disease in Lambeth. A community study of prevalence and use of medical care. British journal of preventive & social medicine, 30(2), 107–114. https://doi.org/10.1136/jech.30.2.107

Ren, Y., Yang, S., Xu, S., Gao, M., Huang, W., Gao, T., Fang, Q., Quan, C., Zhang, C., Sun, L., Liang, Y., Han, J., Wang, Z., Zhang, F., Zhou, Y., Liu, J., & Zhang, X. (2009). Genetic variation of promoter sequence modulates XBP1 expression and genetic risk for vitiligo. PLoS genetics, 5(6), e1000523. https://doi.org/10.1371/journal.pgen.1000523

Richmond, J. M., & Harris, J. E. (2014). Immunology and skin in health and disease. Cold Spring Harbor perspectives in medicine, 4(12), a015339. doi:10.1101/cshperspect.a015339

Roan, F., Obata-Ninomiya, K., & Ziegler, S. F. (2019). Epithelial cell–derived cytokines: more than just signaling the alarm. Journal of Clinical Investigation, 129(4), 1441–1451. doi: 10.1172/jci124606

Robbins, S. L., Aster, J. C., Perkins, J. A., Cotran, R. S., Kumar, V., & Abbas, A. K. (2015). Robbins and Cotran Pathologic Basis of Disease. Philadelphia: Elsevier/Saunders.

Rosenbaum, B. E., Klein, R., Hagan, P. G., Seadey, M. Y., Quarcoo, N. L., Hoffmann, R., … Leger, M. C. (2017). Dermatology in Ghana: a retrospective review of skin disease at the Korle Bu Teaching Hospital Dermatology Clinic. The Pan African medical journal, 26, 125. doi:10.11604/pamj.2017.26.125.10954

Safety and Efficacy of Nail Products. (2017). Cosmetics, 4(3), 24. doi:10.3390/cosmetics4030024

Sánchez-Borges, M., Capriles-Hulett, A., & Caballero-Fonseca, F. (2015). Demographic and clinical profiles in patients with acute urticaria. Allergologia et immunopathologia, 43(4), 409–415. https://doi.org/10.1016/j.aller.2014.04.010

Sardana, K., Mahajan, S., Sarkar, R., Mendiratta, V., Bhushan, P., Koranne, R. V., & Garg, V. K. (2009). The spectrum of skin disease among Indian children. Pediatric dermatology, 26(1), 6–13. https://doi.org/10.1111/j.1525-1470.2008.00814.x

Schallreuter, K. U., Moore, J., Wood, J. M., Beazley, W. D., Gaze, D. C., Tobin, D. J., Marshall, H. S., Panske, A., Panzig, E., & Hibberts, N. A. (1999). In vivo and in vitro evidence for hydrogen peroxide (H2O2) accumulation in the epidermis of patients with vitiligo and its successful removal by a UVB-activated pseudocatalase. The journal of investigative dermatology. Symposium proceedings, 4(1), 91–96. https://doi.org/10.1038/sj.jidsp.5640189

Schmidt, A., Karrasch, T., Thomalla, M., Schlegel, J., Salzberger, B., Schäffler, A., & Hanses, F. (2017). Innate Immunity of Adipose Tissue in Rodent Models of Local and Systemic Staphylococcus aureus Infection. Mediators of inflammation, 2017, 5315602. doi:10.1155/2017/5315602

Schmidt, M., Raghavan, B., Müller, V., Vogl, T., Fejer, G., Tchaptchet, S., Keck, S., Kalis, C., Nielsen, P. J., Galanos, C., Roth, J., Skerra, A., Martin, S. F., Freudenberg, M. A., & Goebeler, M. (2010). Crucial role for human Toll-like receptor 4 in the development of contact allergy to nickel. Nature immunology, 11(9), 814–819. https://doi.org/10.1038/ni.1919

Schwartz, R. A., Janusz, C. A., & Janniger, C. K. (2006). Seborrheic dermatitis: an overview. American family physician, 74(1), 125–130.

Seth, D., Cheldize, K., Brown, D., & Freeman, E. F. (2017). Global Burden of Skin Disease: Inequities and Innovations. Current dermatology reports, 6(3), 204–210. doi:10.1007/s13671-017-0192-7

Shane, H. L., Long, C. M., & Anderson, S. E. (2019). Novel cutaneous mediators of chemical allergy. Journal of immunotoxicology, 16(1), 13–27. https://doi.org/10.1080/1547691X.2018.1515279

Shklovskaya, E., O'Sullivan, B. J., Ng, L. G., Roediger, B., Thomas, R., Weninger, W., & Fazekas de St Groth, B. (2011). Langerhans cells are precommitted to immune tolerance induction. Proceedings of the National Academy of Sciences of the United States of America, 108(44), 18049–18054. doi:10.1073/pnas.1110076108

Silva de Castro, C. C., do Nascimento, L. M., Walker, G., Werneck, R. I., Nogoceke, E., & Mira, M. T. (2010). Genetic variants of the DDR1 gene are associated with vitiligo in two independent Brazilian population samples. The Journal of investigative dermatology, 130(7), 1813–1818. https://doi.org/10.1038/jid.2010.34

Singh, A., Sharma, P., Kar, H. K., Sharma, V. K., Tembhre, M. K., Gupta, S., Laddha, N. C., Dwivedi, M., Begum, R., Indian Genome Variation Consortium, Gokhale, R. S., & Rani, R. (2012). HLA alleles and amino-acid signatures of the peptide-binding pockets of HLA molecules in vitiligo. The Journal of investigative dermatology, 132(1), 124–134. https://doi.org/10.1038/jid.2011.240

Singh, T. P., Zhang, H. H., Borek, I., Wolf, P., Hedrick, M. N., Singh, S. P., Kelsall, B. L., Clausen, B. E., & Farber, J. M. (2016). Monocyte-derived inflammatory Langerhans cells and dermal dendritic cells mediate psoriasis-like inflammation. Nature communications, 7, 13581. https://doi.org/10.1038/ncomms13581

Smith, F., Irvine, A., Terron-Kwiatkowski, A. et al. (2006). Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. Nat Genet 38, 337–342. https://doi.org/10.1038/ng1743

So, J.K., Hamstra, A., Calame, A. et al. (2015). Another Great Imitator: Allergic Contact Dermatitis Differential Diagnosis, Clues to Diagnosis, Histopathology, and Treatment. Curr Treat Options Allergy 2, 333–348. https://doi.org/10.1007/s40521-015-0064-y

Speeckaert, R., Speeckaert, M. M., & van Geel, N. (2015). Why treatments do(n't) work in vitiligo: An autoinflammatory perspective. Autoimmunity reviews, 14(4), 332–340. https://doi.org/10.1016/j.autrev.2014.12.003

Statescu, L., Branisteanu, D., Dobre, C., Solovastru, L. G., Vasilca, A., Petrescu, Z., & Azoicai, D. (2011). Contact dermatitis - epidemiological study. Maedica, 6(4), 277–281.

Stevanović, S., Draper, L. M., Langhan, M. M., Campbell, T. E., Kwong, M. L., Wunderlich, J. R., Dudley, M. E., Yang, J. C., Sherry, R. M., Kammula, U. S., Restifo, N. P., Rosenberg, S. A., & Hinrichs, C. S. (2015). Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 33(14), 1543–1550. https://doi.org/10.1200/JCO.2014.58.9093

Stone, K. M., Karem, K. L., Sternberg, M. R., McQuillan, G. M., Poon, A. D., Unger, E. R., & Reeves, W. C. (2002). Seroprevalence of human papillomavirus type 16 infection in the United States. The Journal of infectious diseases, 186(10), 1396–1402. https://doi.org/10.1086/344354

Subramanian, I., Singh, V. K., & Jere, A. (2018). Elucidating mechanistic insights into drug action for atopic dermatitis: a systems biology approach. BMC dermatology, 18(1), 3. https://doi.org/10.1186/s12895-018-0070-4

Tabutin D. (1991). La croissance demographique de l'Afrique: bilan et perspectives [African population growth: status and prospects]. Revue tiers-monde, 32(125), 159–173.

Taïeb, A., Picardo, M., & VETF Members (2007). The definition and assessment of vitiligo: a consensus report of the Vitiligo European Task Force. Pigment cell research, 20(1), 27–35. https://doi.org/10.1111/j.1600-0749.2006.00355.x

Tay, Y. K., Kong, K. H., Khoo, L., Goh, C. L., & Giam, Y. C. (2002). The prevalence and descriptive epidemiology of atopic dermatitis in Singapore school children. The British journal of dermatology, 146(1), 101–106. https://doi.org/10.1046/j.1365-2133.2002.04566.x

Taylor S. C. (2003). Epidemiology of skin diseases in ethnic populations. Dermatologic clinics, 21(4), 601–607. https://doi.org/10.1016/s0733-8635(03)00075-5

Taylor, S. C. (2011). Treatments for skin of color. Edinburgh: Elsevier Saunders.

Tazi-Ahnini, R., McDonagh, A. J., Wengraf, D. A., Lovewell, T. R., Vasilopoulos, Y., Messenger, A. G., Cork, M. J., & Gawkrodger, D. J. (2008). The autoimmune regulator gene (AIRE) is strongly associated with vitiligo. The British journal of dermatology, 159(3), 591–596. https://doi.org/10.1111/j.1365-2133.2008.08718.x

Tindle R. W. (2002). Immune evasion in human papillomavirus-associated cervical cancer. Nature reviews. Cancer, 2(1), 59–65. https://doi.org/10.1038/nrc700

Toomey, C. B., Cauvi, D. M., Hamel, J. C., Ramirez, A. E., & Pollard, K. M. (2014). Cathepsin B regulates the appearance and severity of mercury-induced inflammation and autoimmunity. Toxicological sciences : an official journal of the Society of Toxicology, 142(2), 339–349. doi:10.1093/toxsci/kfu189

Trinh, H. K., Pham, D. L., Ban, G. Y., Lee, H. Y., Park, H. S., & Ye, Y. M. (2016). Altered Systemic Adipokines in Patients with Chronic Urticaria. International archives of allergy and immunology, 171(2), 102–110. https://doi.org/10.1159/000452626

Tsepkolenko, A., Tsepkolenko, V., Dash, S., Mishra, A., Bader, A., Melerzanov, A., & Giri, S. (2019). The regenerative potential of skin and the immune system. Clinical, cosmetic and investigational dermatology, 12, 519–532. doi:10.2147/CCID.S196364

Türsen, U., Kaya, T. I., Erdal, M. E., Derici, E., Gündüz, O., & Ikizoğlu, G. (2002). Association between catechol-O-methyltransferase polymorphism and vitiligo. Archives of dermatological research, 294(3), 143–146. https://doi.org/10.1007/s00403-002-0295-1

Ugbomoiko, U., Oyedeji, S., Babamale, O., & Heukelbach, J. (2018). Scabies in Resource-Poor Communities in Nasarawa State, Nigeria: Epidemiology, Clinical Features and Factors Associated with Infestation. Tropical Medicine and Infectious Disease, 3(2), 59. doi:10.3390/tropicalmed3020059

Ukonu, A. B., & Eze, E. U. (2012). Pattern of skin diseases at University of Benin teaching hospital, Benin city, Edo State, South-South Nigeria: a 12 month prospective study. Global journal of health science, 4(3), 148-57. doi:10.5539/gjhs.v4n3p148

Valladeau, J., Ravel, O., Dezutter-Dambuyant, C., Moore, K., Kleijmeer, M., Liu, Y., … Saeland, S. (2000). Langerin, a Novel C-Type Lectin Specific to Langerhans Cells, Is an Endocytic Receptor that Induces the Formation of Birbeck Granules. Immunity, 12(1), 71–81. doi: 10.1016/s1074-7613(00)80160-0

van den Boorn, J. G., Konijnenberg, D., Dellemijn, T. A., van der Veen, J. P., Bos, J. D., Melief, C. J., Vyth-Dreese, F. A., & Luiten, R. M. (2009). Autoimmune destruction of skin melanocytes by perilesional T cells from vitiligo patients. The Journal of investigative dermatology, 129(9), 2220–2232. https://doi.org/10.1038/jid.2009.32

Voehringer D. (2017). Recent advances in understanding basophil functions in vivo. F1000Research, 6, 1464. https://doi.org/10.12688/f1000research.11697.1

Wakim, L. M., Waithman, J., van Rooijen, N., Heath, W. R., & Carbone, F. R. (2008). Dendritic cell-induced memory T cell activation in nonlymphoid tissues. Science (New York, N.Y.), 319(5860), 198–202. https://doi.org/10.1126/science.1151869

Weaver, C. T., Hatton, R. D., Mangan, P. R., & Harrington, L. E. (2007). IL-17 family cytokines and the expanding diversity of effector T cell lineages. Annual review of immunology, 25, 821–852. https://doi.org/10.1146/annurev.immunol.25.022106.141557

Webster, G. F. (2014). Inflammation in Acne. Pathogenesis and Treatment of Acne and Rosacea, 97-101. doi:10.1007/978-3-540-69375-8_12

Wedi, B., Raap, U., Wieczorek, D., & Kapp, A. (2009). Urticaria and infections. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology, 5(1), 10. https://doi.org/10.1186/1710-1492-5-10

White G. M. (1998). Recent findings in the epidemiologic evidence, classification, and subtypes of acne vulgaris. Journal of the American Academy of Dermatology, 39(2 Pt 3), S34–S37. https://doi.org/10.1016/s0190-9622(98)70442-6

Wilgus, T. A., Roy, S., & McDaniel, J. C. (2013). Neutrophils and Wound Repair: Positive Actions and Negative Reactions. Advances in wound care, 2(7), 379–388. https://doi.org/10.1089/wound.2012.0383

Willenborg, S., Lucas, T., Loo, G. V., Knipper, J. A., Krieg, T., Haase, I., … Eming, S. A. (2012). CCR2 recruits an inflammatory macrophage subpopulation critical for angiogenesis in tissue repair. Blood, 120(3), 613–625. doi: 10.1182/blood-2012-01-403386.

Winer, R. L., Lee, S. K., Hughes, J. P., Adam, D. E., Kiviat, N. B., & Koutsky, L. A. (2003). Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. American journal of epidemiology, 157(3), 218–226. https://doi.org/10.1093/aje/kwf180

Wolkenstein P, Grob JJ, Bastuji-Garin S et al. French people and skin diseases: results of a survey using a representative sample. Arch Dermatol 2003; 139:1614–19

Woodland DL, Kohlmeier JE. (2009), Migration, maintenance and recall of memory T cells in peripheral tissues. Nature Reviews Immunology, 9(3), 153-61.

Xiao, Y., Williams, J. S., & Brownell, I. (2014). Merkel cells and touch domes: more than mechanosensory functions?. Experimental dermatology, 23(10), 692–695. https://doi.org/10.1111/exd.12456

Yamanaka, K. I., & Mizutani, H. (2011). The role of cytokines/chemokines in the pathogenesis of atopic dermatitis. Current problems in dermatology, 41, 80–92. https://doi.org/10.1159/000323299

Yang, J., Zhao, L., Xu, M., & Xiong, N. (2017). Establishment and function of tissue-resident innate lymphoid cells in the skin. Protein & cell, 8(7), 489–500. doi:10.1007/s13238-017-0388-4

Yang, X. Y., Wu, W. J., Yang, C., Yang, T., He, J. D., Yang, Z., & He, L. (2013). Association of HSD17B3 and HSD3B1 polymorphisms with acne vulgaris in Southwestern Han Chinese. Dermatology (Basel, Switzerland), 227(3), 202–208. https://doi.org/10.1159/000353581

Yoshioka, Y., Kuroda, E., Hirai, T., Tsutsumi, Y., & Ishii, K. J. (2017). Allergic Responses Induced by the Immunomodulatory Effects of Nanomaterials upon Skin Exposure. Frontiers in immunology, 8, 169. doi:10.3389/fimmu.2017.00169

Yotsu RR, Kouadio K, Vagamon B, N'guessan K, Akpa AJ, Yao A, et al. (2018) Skin disease prevalence study in schoolchildren in rural Côte d'Ivoire: Implications for integration of neglected skin diseases (skin NTDs). PLoS Negl Trop Dis 12(5): e0006489. https://doi.org/10.1371/journal.pntd.0006489

Yousef H, Alhajj M, Sharma S. Anatomy, Skin (Integument), Epidermis. [Updated 2020 Jul 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470464/

Zhang, L. J., Guerrero-Juarez, C. F., Hata, T., Bapat, S. P., Ramos, R., Plikus, M. V., & Gallo, R. L. (2015). Innate immunity. Dermal adipocytes protect against invasive Staphylococcus aureus skin infection. Science (New York, N.Y.), 347(6217), 67–71. https://doi.org/10.1126/science.1260972

Zhang, Ling-juan & Chen, Stella & Guerrero-Juarez, Christian & Li, Fengwu & Tong, Yun & Liang, Yuqiong & Liggins, Marc & Chen, Xu & Chen, Hao & Li, Min & Hata, Tissa & Zheng, Ye & Plikus, Maksim & Gallo, Rich. (2018). Age-Related Loss of Innate Immune Antimicrobial Function of Dermal Fat Is Mediated by Transforming Growth Factor Beta. Immunity. 50. 10.1016/j.immuni.2018.11.003.

Zhang, M., Qureshi, A. A., Hunter, D. J., & Han, J. (2014). A genome-wide association study of severe teenage acne in European Americans. Human genetics, 133(3), 259–264. https://doi.org/10.1007/s00439-013-1374-4

Zhou, L., Li, K., Shi, Y. L., Hamzavi, I., Gao, T. W., Henderson, M., Huggins, R. H., Agbai, O., Mahmoud, B., Mi, X., Lim, H. W., & Mi, Q. S. (2012). Systemic analyses of immunophenotypes of peripheral T cells in non-segmental vitiligo: implication of defective natural killer T cells. Pigment cell & melanoma research, 25(5), 602–611. https://doi.org/10.1111/j.1755-148X.2012.01019.x

Zmijewski, M. A., & Slominski, A. T. (2011). Neuroendocrinology of the skin. Dermato-Endocrinology, 3(1), 3-10. doi:10.4161/derm.3.1.14617