Skin Failure: Concept Review and Proposed Model

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Skin failure is increasingly recognized as a clinical syndrome. Like all other organs skin can fail, however experts continue to grapple with definitions, causative factors, and manifestations.[1,2] There are currently a number of overlapping clinical entities that include terminal ulcer terminologies that have not been well defined by rigorous research criteria, and not recognized by all providers and regulatory bodies across the healthcare continuum.[1] Establishing skin failure as an entity by defining contributing factors similar to other organ systems will enable providers to recognize and address it effectively in practice, and assist regulators by recognizing and incorporating these pathophysiologic factors into modification of quality measurement criteria.[2] There is a pressing need to define skin failure as a clinical syndrome and understand its pathophysiology because of its implications for both clinical care and health care policy.

Beginning over three decades ago clinicians have sought to gain clarity on skin failure, offering various hypotheses and nomenclatures regarding its genesis and existence. The search for a solution is challenging because there is no universally accepted skin failure definition, nor is there agreement on clinical manifestations or identified biomarkers. The purpose of this paper is to establish a scientific basis for skin failure by identifying pathophysiologic factors that lead to consequences at the cellular level resulting in disruption of the cutaneous barrier and underlying tissues. The model in Figure presents the synergistic nature of these factors including acute and chronic conditions, and how they act to alter dermal physiology leading to barrier disruption and skin failure. The model does not include wounds related to acute trauma such as lacerations or skin tears, wounds related to malignancy, or factors that impact healing which have been discussed elsewhere.[3] Rather the goal of this paper is to provide a conceptual framework for future discussions and research as well as a path to a clear, unifying classification system that takes into consideration terminologies and diagnoses that fall within the skin failure spectrum.

It should be noted that current definitions of skin failure assume visible changes and/or disruption of the dermal barrier, however this may not be complete. The physiologic processes that lead to skin failure take place before visible disruption appears and may involve tissues below the skin including connective tissue and muscle which are subject to the same stressors.

SKIN FAILURE: CONCEPTS AND CONTROVERSIES

A definition for skin failure was initially proposed by Irvine in 1991: "Skin failure could be defined as a loss of normal temperature control with inability to maintain the core temperature, failure to prevent percutaneous loss of fluid, electrolytes and protein with resulting imbalance and failure of the mechanical barrier to penetration by foreign materials."[4] He proposed that skin failure is an entity equivalent to failure of other organs such as heart, lungs, and kidney.[4] He included etiologies such as thermal burns, dermatologic conditions including erythroderma, toxic epidermal necrolysis, and Stevens-Johnson syndrome but did not mention pressure injuries as a manifestation of skin failure.[4]

The next contribution to the definition of skin failure was offered by Langemo and Brown in 2006 as "…an event in which the skin and underlying tissue die due to hypoperfusion that occurs concurrent with severe dysfunction or failure of other organ systems."[5] They postulated the existence of acute skin failure occurring with critical illness, chronic skin failure concurrent with chronic disease states, and end-stage skin failure occurring at the end of life, with hypoperfusion as the primary cause.[5] Langemo's definition was expanded by Levine (2017) who stated, "Skin failure is the state in which tissue tolerance is so compromised that cells can no longer survive in zones of physiological impairment that includes hypoxia, local mechanical stresses, impaired delivery of nutrients, and buildup of toxic metabolic byproducts."[2] He further acknowledged that skin failure could be acute or chronic, whereby chronic skin failure is characterized by disruptions in skin integrity that fail to heal or regenerate in a normal sequential manner to regain structure and function.

Langemo and Brown also postulated the existence of acute skin failure occurring with critical illness, chronic skin failure concurrent with chronic disease states, and end-stage skin failure occurring at the end of life.[5] Hypoperfusion

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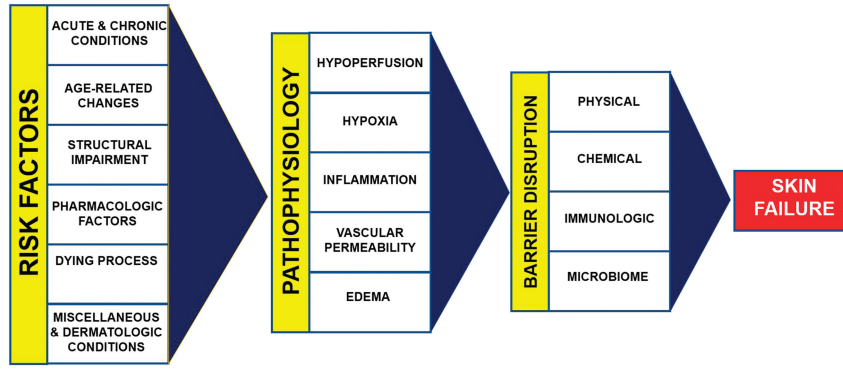
Figure. RISK FACTORS AND PATHOPHYSIOLOGIC CHANGES RESULTING IN DERMAL BARRIER DISRUPTION AND SKIN FAILURE



was noted as the primary cause of each of these entities.[5] Delmore and Cox furthered the acute skin care definition through their research.[6,7] Like Langemo and Brown, Delmore and Cox stated that acute skin failure is a complex phenomenon distinct from a pressure injury.[5–7] They postulated that the main etiology is attributable to failure of the skin and/or supporting structures (e.g., subcutaneous tissue, muscle) due to diseases and conditions during critical illness.[7]

Within the dermatologic literature, acute skin failure is recognized as a life-threatening situation with single organ genesis requiring immediate treatment.[8–10] These diagnoses share a series of events that result in involvement of the entire body with consequences that include hemodynamic changes, impaired thermoregulatory control, and metabolic complications.[8–10]

Several authors have proposed a variety of terminologies and clinical syndromes which fall within the spectrum of skin failure. These include the Kennedy Terminal Ulcer (KTU), Trombley Brennan Terminal Tissue Injury (TBTTI), Skin Failure at Life's End (SCALE), and unavoidable pressure injury.[1,11–13] In a review of terminal ulcer terminology, Levine pointed out intrinsic weaknesses that include conflation of separate concepts of diagnosis and prognosis, wide spectrum of definitions of the end-of-life period, and lack of accuracy in predicting death.[14] Adding to the confusion, the term acute skin failure which commonly occurs in critical care situations is often used interchangeably with the more general term of skin failure.[15–17]

The distinction between skin failure and pressure injury remains controversial.[6,15–20] In 2010, experts at a consensus conference hosted by the National Pressure Ulcer Advisory Panel (NPUAP – since renamed National Pressure Injury Advisory Panel - NPIAP), defined the unavoidable pressure injury as one that may occur even though providers have evaluated the individual's clinical condition, risk factors have been evaluated and defined, and interventions have been implemented that are consistent with individual needs, goals, and recognized standards of practice.[21] Adding further complexity is the fact that Centers for Medicare and Medicaid Services (CMS) adopted the concept of unavoidable pressure injuries and terminal ulcers in regulations governing skilled nursing facilities, while there are no similar guidelines in acute care environments.[22] This disparate array of regulations is perplexing, as human disease follows the same pathologic and physiologic principles across the healthcare continuum. In addition, pressure injuries are a commonly designated quality indicator.[23] A determination of quality deficit brings adverse consequences including dissatisfied patients, regulatory citations, and risk management issues, all of which may not be warranted if the quality indicator is faulty or inadequately defined.

The focus should be on the primary etiology of a wound – whether it occurred due to pressure forces or a combination of pathophysiological factors leading to skin failure. Proper prevention strategies should always be applied based on a patient's risk factors, and wounds occurring from inadequate prevention strategies should not be labeled as skin failure or acute skin failure. When it has been deemed that all possible strategies have been applied and a wound still evolves, the next step is to determine the primary etiology.

THE SKIN: BARRIER FUNCTION AND BIOMARKERS

Before identifying and discussing risk factors and physiologic consequences, a brief review of dermal anatomy and physiology is necessary to provide context for a discussion on skin failure. The skin is the largest and an arguably the most complex organ with multiple functions that are summarized in Table 1, not all of which pertain to the model. The discussion on skin failure concentrates primarily on physical, chemical, immunologic, and microbiome barrier functions, all of which are intertwined to protect the organism.[24–26] The physical barrier is composed of various anatomic levels of skin that include the system of tight

Table 1. ORGAN FUNCTIONS OF SKIN

Function	Description
Physical barrier	This is localized primarily in the anucleated stratum corneum and nucleated epidermis, which contains tight cellular junctions and lipid rich extracellular layers, keratin filaments, and macrofibrils.
Chemical barrier	Maintains moisture and acid mantle of the promoting commensal bacteria and inhibiting pathogens.
Immunologic barrier	Immunologic defenses composed of the cellular and humoral elements including Langerhans cells, B and T lymphocytes, complement system, antimicrobial peptides, and dendritic cells.
Microbiome barrier	Skin is colonized by a variety of microorganisms that are either symbiotic (each organism benefits) or commensal (one organism benefits). These organisms have roles in the cutaneous immune system and inhibiting pathogens.
Thermoregulation	The skin regulates body temperature with its blood supply. Dilated vessels allow for heat loss while constricted vessels retain heat.
Osmoregulation	The process of maintaining salt and water balance through sweat glands.
Endocrine function	Vitamin D3 is produced in the skin, and sebaceous glands are important in testosterone metabolism. The skin is also rich in glucocorticoid, thyroid, and estrogen receptors.
BP maintenance	Peripheral vascular resistance in the skin's extensive arterioles and capillary beds has a dynamic role in cardiovascular dynamics by maintaining BP.
Sensory function	Skin facilitates the perception of many sensations. Sensory receptors are divided into mechanoreceptors, thermoreceptors, nociceptors (pain sensation), and pruriceptors (itch sensation).
Socialization and reproduction	Social engagement starts at birth with skin-to-skin contact when the baby is made to feel part of a family. Skin tone as genetically manifested by melanocytes can determine ethnic or racial experience in life. As an external organ, skin sends signals of physical attractiveness that are often critical in human reproduction.

Adapted from Levine JM. Clinical aspects of aging skin: considerations for the wound care practitioner. Adv Skin Wound Care 2020;33(1):12-9.

junctions between cells in the stratum corneum and the complex vascular structures that supply oxygen and nutrients and remove waste. The immune barrier is composed of resident immune cells that sense microbial danger signals, initiate immune response, and trigger inflammation. The chemical barrier is composed of sebum which contains triglycerides and cholesterols as well as an acidic surface pH, all of which maintains natural moisturization. The microbiome barrier is a microbial community that includes commensal bacteria and fungi that control potential pathogens. The accrual of underlying illnesses and concomitant physiologic aberrancies weakens barrier function of the skin and can result in skin failure.

Despite its size and complexity, and in contrast with other organ systems, there are currently no reliable biomarkers to measure skin failure. For example, congestive heart failure can be measured by ejection fraction, presence of left ventricular hypertrophy, and elevated central venous pressure. Renal failure can be measured with blood urea nitrogen (BUN), creatine, and glomerular filtration rate (GFR). Biliary failure can be measured with ammonia level, international normalized ratio (INR), and bilirubinemia. The absence of biomarkers should not prevent clinicians from diagnosing skin failure if clinical criteria are defined and recognized. There is thus an urgent need to recognize the existence of skin failure, define clinical criteria, and identify biomarkers.

SKIN FAILURE AND REGIONAL VARIATIONS IN ANATOMY AND PERFUSION

The argument has been made that the diagnosis of skin failure is not possible when manifestations are limited to specific portions of the body, and not generalized to the entire organ such as occurring in dermatologic conditions such as Stevens-Johnson syndrome or toxic epidermal necrolysis.[27] A corollary of this argument is the assumption that skin failure and pressure injuries are separate entities. This argument does not hold up when taking into consideration regional variations in skin anatomy and physiology, and how these variations alter the response to regional physiologic and mechanical stressors, particularly in the setting of advanced age and/or comorbid conditions impacting anatomy and physiology of skin.

There are striking regional anatomical variations that include epidermal thickness, pigmentation, frequency of appendages such as pilosebaceous units and eccrine glands, concentration of melanocytes, presence of smooth muscle, structure of dermal papillae, thickness of fat layer, presence of nerve endings, density of capillaries and other vascular structures, and others.[28–30] These regional variations are genetically programmed in positional codes that arise during embryonic development, and manifest in a level of anatomic and physiologic complexity beyond what is represented diagrammatically in cross sections of skin commonly found in textbooks.

Regional differences are also impacted by aging and disease, increasing the propensity to develop local areas of skin failure. Aging for example results in thinning, loss of vascularity, disordered collagen and elastin, decreased immune function, and other physical changes that result in increased fragility and susceptibility to stress and hypoxic damage (see Table 3).[31] In addition, certain drugs and other therapeutics such as radiation therapy can alter and

Table 2. CUTANEOUS FUNCTIONS THAT DECLINE WITH AGE AND INCREASE BARRIER VULNERABILITY

Immune response
Cellular replacement
Injury response
Dermal clearance
Vascular response
Sebum production
Sweat production
Thermoregulation
Sensory perception
Vitamin D production

Adapted from Levine JM. Clinical aspects of aging skin: considerations for the wound care practitioner. Adv Skin Wound Care 2020;33(1):12-9.

impair anatomy and physiology of skin, as well as disease processes that affect macro- and microvasculature.

The sacrococcygeal and heel areas are unique in their circulation and structure compared to the rest of the body, rendering them more prone to skin failure in the presence of multiple synergist comorbidities and chronic conditions. The sacrococcygeal, buttocks and ischium differ in circulation and tissue composition. Of these areas, the sacrococcygeal area is more compromised than buttocks and ischium.[32] Circulation and elastic fibers allow tissue recovery after deformation and sacral skin has adequate capillary density but less elastic fibers.[32] This imbalance can delay tissue recovery and when significant comorbidities are present that decrease tissue oxygenation and perfusion, the response and recovery time will be delayed.[32–35] The heel area suffers the same fate and is equally vulnerable to ischemic damage.[6,8] The posterior calcaneus is a large bone with relatively little covering skin and subcutaneous tissue that receives its blood supplies from collateral circulation.[6,36–39]

The body has been described as a three-dimensional jigsaw supplied by source arteries responsible for perfusion of skin and underlying structures, with composite units termed angiosomes.[40] When a disease process such as atherosclerosis impairs flow of a specific artery, the areas of skin perfused by that artery will be more prone to failure than others.[41] When additional comorbidities are superimposed such as microvascular disease from diabetes mellitus, anemia, edema, or anasarca, the susceptibility of these areas to hypoperfusion is further increased. Other sources of tissue deformation, particularly in the context of multiple physiological aberrancies will accelerate the process of local skin failure.

SKIN FAILURE: PATHOPHYSIOLOGIC FACTORS

There are several pathophysiologic factors which lends credence to the theory that skin failure and acute skin failure are the result of multiple acute and chronic conditions as well as other comorbid conditions.[6,7,16,17] These include hypoperfusion, hypoxia, inflammation, vascular permeability and edema. Skin failure may include levels of tissue that are adjacent and/or below affect the skin share similar dependence on oxygen, nutrients and intact structural anatomy. Hence, skin failure can be conceptualized as a local or widely distributed phenomenon. Risk factors act synergistically, creating an array of pathophysiologic aberrancies leading skin failure or acute skin failure in critical care and other settings (see Figure).

Hypoperfusion

Hypoperfusion is simply decreased blood flow to an organ.[41] Hypoperfusion has multiple causes including decreased cardiac output, decreased oxygen carrying capacity of the blood, and obstruction of vasculature. In hypotension or low cardiac output states, the ability to perfuse tissues and organs becomes compromised. Diseases such as valvular disorders, congestive heart failure, cardiac arrhythmias, cardiac tamponade, shock, and large volume blood loss will reduce cardiac output, decreasing the ability to maintain blood pressure.[42] Failure of the cardiovascular system to perfuse tissue leads to dysfunction in cellular metabolism and impairment in both oxygen and glucose use.[43] Respiratory failure can result in hypoperfusion when pulmonary function is compromised. Anemia is a state of reduced oxygen carrying capacity of the blood that contributes to impaired tissue perfusion. Hypoperfusion can influence tissue oxygen levels thus is associated with hypoxia.

Hypoxia

Hypoxia is present when insufficient oxygen leads to failure of homeostasis.[44] When oxygen delivery is impaired, a detrimental physiologic cascade occurs at the cellular level that includes membrane instability, cellular edema, and intracellular acidosis caused by the switch to

Table 3. CELLULAR ELEMENTS OF THE DERMAL IMMUNE SYSTEM DISPLAYING THE COMPLEXITY OF THE SKIN

Keratinocytes
Dendritic cells
Monocytes
Macrophages
Granulocytes
Mast cells
Vascular and lymphatic endothelial cells
T lymphocytes

Adapted from Bos JD, Luiten RM. Skin immune system. Cancer Treat Res 2009;146:45-62.

anaerobic metabolism, including release of hypoxia-inducible factor (HIF-1α).[45] On the cellular level, impaired oxygen utilization forces cells to switch from aerobic metabolism to anaerobic metabolism resulting in a deficit of adenosine triphosphate (ATP) production and cellular edema.[43] Anaerobic metabolism affects the pH by producing lactate leading to metabolic acidosis. As blood pH decreases, reduced oxygen-carrying capacity in the blood ensues. In severe low output states such as shock, blood is shunted from the peripheral circulation in an effort to improve oxygenation and perfusion to the central vital organs, which in turn compromises perfusion to skin including at-risk anatomical areas such as buttocks, coccyx, sacrum, ischia and heels. Moreover, impaired tissue perfusion impedes the skin's tolerance for pressure by forcing capillaries to close at lower interface pressures.[46]

Both macrovascular and microvascular disease contribute to hypoperfusion, and hypertension, hyperlipidemia, and diabetes mellitus are important risk factors. Diabetes mellitus, particularly when poorly controlled, results in a spectrum of vascular disease that includes reduced vasodilatation, and micro- and macrovascular impairment resulting in local hypoxia and poor tissue perfusion.[47,48] The relationship of hypoxia and inflammation has been linked to many conditions including certain cancers, infection and acute pulmonary conditions.[49]

Inflammation

The inflammatory response can be acute or chronic, and serves as a protective mechanism to destroy pathogens, trigger adaptive immunity, and initiate healing.[50] Although inflammation is protective, it contains a pathological capacity that can cause damage to living tissue adversely affecting the vascular endothelium, increasing permeability and impairing function of the dermal barrier and underlying tissue[51,52] In turn, this causes edema, structural compromise, and decreased delivery of nutrients and removal of waste products, thereby elevating the risk for skin failure.

Inflammation is activated by injury in vascularized tissue by conditions including infection, ischemia, physical and chemical injuries. Acute inflammation induces a rapid onset of changes to microcirculation that includes hemostasis, vasodilation, increased vascular permeability causing fluid leakage into the interstitial space, and white blood cell adhesion.[43] Chronic inflammation can occur as a result of an unsuccessful acute inflammatory response, or as a distinct clinical process with insidious onset, prolonged course and slow resolution.[53] Most chronic illnesses including cardiac disease, neurologic disorders, malignancies, infectious states, and diabetes manifest a component of inflammation.[54] Both hyperglycemia and aging are associated with increased levels of inflammation that cause accelerated damage to tissue.[47,55]

Increased Vascular Permeability

Increased vascular permeability occurs with an array of comorbidities resulting in leakage of fluid into the interstitial space.[56] Capillary walls consist of a single layer of flattened endothelial cells that constitute a dynamic barrier between the blood and surrounding tissue. Other components include the basement membrane, extracellular matrix, and endothelial glycocalyx which is a mesh-like matrix that prevents proteins from passing into the interstitium. Regulation of vascular permeability is dependent upon interaction of intrinsic and extrinsic factors and inflammatory mediators.[57] Both inflammation and hypoalbuminemia cause increased vascular permeability.[58]

Vascular permeability is influenced by blood pressure and molecular regulators such as growth factors and inflammatory mediators.[59] Physiological insults such as burns, hemorrhage, sepsis, and fluid resuscitation result in derangement of the microvascular barrier. Several disease states causing vascular hyperpermeability include infections, diabetes mellitus, immune disorders, and cancer, as well as age-dependent alterations in basement membrane thickness.[60] The presence of these preexisting conditions sets the stage for accelerated vascular hyperpermeability with a predisposition for skin failure due to structural compromise, impaired oxygen and nutrient transport, and inability to remove waste.

Edema

Edema represents structural compromise as it is an abnormal accumulation of fluid either within cells or in the interstitial space, thereby increasing the diffusion distance for delivery of oxygen and other nutrients and limiting waste removal.[61] There are two types of edema: intracellular edema and interstitial edema.[62] Intracellular edema is primarily a consequence of ischemia, while interstitial edema is caused by increased hydrostatic pressure, decreased colloid osmotic pressure, and impaired lymphatic drainage.[62] Both are recognized as contributory to the development of pressure injuries and deep tissue injury.[62]

Edema and its extreme form anasarca has multiple causes including decreased plasma oncotic pressure from hypoalbuminemia, increased plasma volume, increased vascular permeability, and lymphatic obstruction as well as illnesses including liver disease, congestive heart failure, renal disease, malignancies, and others.[61] Medications that worsen edema including estrogens, antihypertensives, thiazolidinediones, corticosteroids, calcium channel blockers and nonsteroidal anti-inflammatory drugs (NSAIDs).[63]

Hypoalbuminemia is a common cause of edema due to loss of oncotic pressure and has many contributing factors including malnutrition, nephrotic syndrome, liver

failure, chronic renal or hepatic disease, protein losing enteropathies, and inflammatory states.[64] Serum albumin level can drop precipitously in the setting of inflammation, and is therefore designated as a negative acute phase reactant.[65,66] Whatever the cause, edema distorts tissue architecture, impedes nutrient delivery and waste removal, and increases susceptibility to skin failure.[67]

In summary, an array of underlying pathophysiologic factors can lead to skin failure in a synergistic fashion. For example, patients with acute pulmonary conditions can experience simultaneous inflammation, hypoxia, hypoperfusion and edema.[68] Moreover, inflammation results in increased vascular permeability which manifests as edema.[69] Skin failure is therefore a complex phenomenon reflective of multiple pre-existing conditions and cellular interactions.

ACUTE AND CHRONIC CONDITIONS

A number of acute and chronic conditions produce physiologic effects that promote or facilitate disruption of the cutaneous barrier and underlying tissues. This section provides examples, illustrating how they cause physiologic aberrancies leading to skin failure. We note that there are complex multifactorial conditions that may not fall into a single physiologic classification leading to skin failure, including changes with age and the dying process.

Multiple Organ Dysfunction Syndrome

Multiple organ dysfunction syndrome (MODS) is the progressive dysfunction of two or more organs as a result of a massive inflammatory response caused by a severe illness or injury.[70] MODS can result from an infectious process such as septic shock or non-infectious conditions such massive trauma, or circulatory collapse.[71] A major feature of MODS is maldistribution of blood flow, endothelial disruption, and hypermetabolic state with inadequate oxygen delivery to the tissues.[43] An imbalance in the demand for oxygen and widespread hypoxia to body tissues and organs results in cellular acidosis, impaired cellular function, and increased risk for skin failure. Many of these characteristics are shared by Systemic Inflammatory Response Syndrome (SIRS) and severe sepsis, both of which manifest systemic inflammation and increased capillary permeability. As discussed by Langemo et al, skin as an organ is subject to failure.[5] Therefore, as the largest organ of the body, acute skin failure should be considered in the spectrum of MODS.

Skin injuries with MODS have been reported by several investigators.[6,7,16,17] Recent investigations examining acute skin failure in critically ill patients found failure of two organs (lung and liver) to be significantly associated with the development of acute skin failure.[6,15–17] In a follow-up study Delmore et al. found respiratory and renal failure predictive of acute skin failure.[7]

Protein-Calorie Malnutrition

It is well established that protein calorie malnutrition (PCM) impacts the skin's barrier function and protective mechanisms, and plays a key role in both frailty and sarcopenia.[72,73] Malnutrition results from inadequate intake of protein, calories, and micronutrients as well as hypermetabolism or negative nitrogen balance from disease-associated inflammation and other mechanisms.[74,75] This becomes a vicious cycle as inflammation potentiates PCM from anorexia and decreased food intake with elevation of resting energy expenditure and increased muscle catabolism.[74] PCM is usually accompanied by decreased body weight, muscle mass, and subcutaneous fat, localized or generalized fluid accumulation (edema), and diminished functional status.[74,75] Any condition that results in inflammatory, hypermetabolic and/or hypercatabolic states will increase the risk for malnutrition and impair the body's response to nutrition interventions.[74–76]

PCM along with accompanying micronutrient deficiencies, negative nitrogen balance, and other imbalances creates a state whereby the skin has the inability to respond adequately to physiologic stressors.[77] PCM therefore promotes skin failure by attacking all levels of the cutaneous barrier via multiple physiologic mechanisms including hypoalbuminemia, edema, vascular leakage, immune compromise, and hypoperfusion. A state is thereby created that impairs the skin's ability to respond appropriately to challenges including hypoperfusion and structural impairment, and will increase vulnerability to skin failure.

Immunocompromised States

The immune system is an integral component of the dermal barrier both for prevention of infection and structural maintenance.[24] There are multiple components of the dermal immune system including biomolecules and pH regulation, cell mediated and humoral immunity, and maintenance of the microbiome.[78,79] When tissue becomes vulnerable, stressed, damaged, or invaded by pathogenic microorganisms the immune system steps in to prevent further damage and initiate the process of healing.

Protective biomolecules include antimicrobial peptides (AMPs) and lipids which participate in skin defense by disrupting bacterial membranes.[79] The pH of human skin is slightly acidic, rendering it inhospitable for pathogens and assisting to maintain a commensal and protective microbiome.[80] An array cellular and humoral constituents protect and promote tissue function and act as sentinels by actively sampling environmental antigens.[78,79] Cellular elements, which are only a partial component of the skin's immune system, are presented in Table 2.

Because of its inherent complexity, compromise of the immune system can occur via multiple mechanisms, and in concert with other physiologic stressors can lead to

skin failure. Causes can include infectious diseases such as HIV, autoimmune diseases, pharmacologic factors such as steroids, immunomodulators, cancer chemotherapies, and changes with age.[81–83] Diabetes mellitus is a disease commonly associated with altered immune response resulting from glycosylation of immunoglobulins and leukocyte dysfunction leading to lower resistance to infection which further accelerates skin breakdown and impairs healing.[47] Immunocompromise via multiple mechanisms therefore impacts integrity of the cutaneous barrier, rendering susceptibility to skin failure.

AGE-RELATED CHANGES

There are acute and chronic conditions that may not fall into a single physiologic classification leading to skin failure, including changes with age and the dying process, but have a common denominator in increasing the vulnerability of skin. As a complex organ with multiple functions, multiple physiological aberrations can adversely affect these functions from a variety of pathways. For example, a central discussion in geriatrics is differentiation between changes with age and changes associated with specific diseases.[84] "Homeostenosis" is an older term that references increased vulnerability to disease that occurs with aging due to decreased physiologic reserve.[85] This concept has subsequently been subsumed into the evolving concept of frailty which is addressed below.[86]

Changes with age are both intrinsic and extrinsic, and cause both structural and physiologic compromise that increase the vulnerability of skin (see Table 2).[31] These include decreased vascularity, decreased pilosebaceous units, alterations in surface pH, thinning, flattening of the dermal-epidermal junction, and decreased immune cells.[31] Altered biochemical processes include decreased synthesis and disorganization of collagen and elastin, and decreased synthesis of surface lipids.[31] The cumulative result is decreased homeostasis and increased risk for damage which can begin the process of skin failure.[31]

Frailty and sarcopenia are conditions associated with aging that share components of malnutrition, decline in function, and increased risk for mortality.[73,87] Frailty is characterized by decreased functional reserve and ability to respond to physiologic stressors, resulting in greater vulnerability and increased risk for adverse outcomes.[88] It is postulated that frailty represents a final common pathway that manifests in cognitive and functional decline, disability, falls, failure-to-thrive, pressure injuries, institutionalization, prolonged hospital stay, readmissions, and risk of death.[89,90] Sarcopenia is associated with a progressive and generalized loss of skeletal muscle mass and function, and many authorities consider sarcopenia to be a cause of frailty.[87,91] Components of sarcopenia include increased inflammatory cytokines, reduced food intake, decreased blood flow to muscle and age-related decline in anabolic hormones such as testosterone, dehydroepiandrosterone (DHEA), growth hormone, and Insulin-like Growth Factor-1 (IGF-1).[92–94] Because of their multifactorial impact on function and nutrition, both frailty and sarcopenia should be considered risk factors for skin failure.

STRUCTURAL IMPAIRMENT

The barrier function of skin requires intact cellular structures and anatomical connections between cells.[24] A number of forces promote or facilitate disruption of the cutaneous barrier and underlying tissues. This section provides examples of structural impairment, illustrating how each promotes cell death and impairs protective function of skin leading to skin failure. It should be noted that our discussion regarding structural impairment does not include acute trauma such as surgical wounds, lacerations, and skin tears.

Cytoskeletal and External Forces

Cells are anatomically and physiologically networked in systems that have the capability to adapt and respond to their internal and external environment.[95] Effective barrier function of skin is dependent upon this intact structure. This adaptability includes the cell cytoskeleton continuously reacting to maintain the cell's shape, morphology and support normal cell functions.[95,96] The cytoskeleton allows for the mechanical stability required to withstand extracellular forces that can cause shear stress and deformation.[95,97] The cytoskeleton can become dysfunctional with external forces causing distortion of tissues leading to cell deformation and loss of integrity, thereby generating a cascade of destruction that leads to apoptosis, or cell death.[98] Tissue deformation as caused by pressure and shear are an important component of pressure injury genesis.[99] Given the well described impact of external deformation and cytoskeletal dysfunction, the authors include this as a factor that impairs structural integrity and increases vulnerability to skin failure.

Moisture

Moisture creates threats to the skin's barrier function that include maceration from prolonged exposure to various sources of moisture or the failure to maintain proper microclimate.[100–102] However, moisture alone is not enough to cause skin damage but rather the chemical content of the moisture and presence of pathogenic microorganisms contributes to impaired skin integrity.[101] The disturbance caused by excessive moisture, the chemical composition of the causative agent, and alteration of the acid-mantle with changes in pH interferes with the ability to suppress bacteria and maintain normal tensile strength.[101] Therefore in the context of skin failure, and similar to external

forces of pressure, shear, and other comorbidities, moisture can synergistically potentiate failure of the skin's protective barrier function.

PHARMACOLOGIC FACTORS

Several pharmaceuticals increase susceptibility to skin failure through a variety of mechanisms including alteration of skin anatomy, decrease in blood perfusion and impaired immune function. Corticosteroids, also known as glucocorticoids, are anti-inflammatory drugs that have the immediate effect of suppressing the immune system. Prolonged systemic or topical administration can lead to irreversible atrophy of the skin. In addition to immune suppression, systemic corticosteroids cause glucose intolerance and edema, both of which can increase vulnerability of skin.[103]

Vasopressors are pharmacologic agents often employed in the setting of hypotension refractory to fluid resuscitation.[104] Vasopressors shunt blood from the skin and peripheral circulation to central vessels by increasing peripheral vascular resistance, and elevate mean arterial pressure (MAP) in shock states.[104] Because of their potent vasoconstrictive action, vasopressor agents have been cited as a contributing factor to the high incidence of pressure injuries reported in critical care.[105–108] Risk may be compounded by administration of more than one pressor agent, refractory hypotension, and prolonged mechanical ventilation.[107,109,110] The plausibility that vasopressors contribute to acute skin failure has been suspected, however currently this lacks empirical evidence. Based on the pharmacodynamics inherent in vasopressors, further study is warranted to explore the relationship between vasopressors and acute skin failure.

Chemotherapeutic agents directed at cancer target rapidly dividing cancer cells at different points in the cell cycle resulting in impaired tumor growth, but adverse events affecting skin are well known.[111] Mechanisms of action vary widely from direct cellular toxicity to altering cutaneous vasculature.[112,113] As a result of these effects on various cells and tissues, chemotherapeutic agents in conjunction with the debility of advanced cancer and other comorbidities can increase risk for skin failure.[114]

Immunomodulators and immunosuppressants are a class of drugs that revolutionized the treatment of inflammatory and autoimmune diseases and assist in the survival of transplanted organs. Mechanisms of action vary, but they share selective inhibition of various aspects of the immune system. Immunosuppressive agents have adverse effects on wound healing, and increase the risk for infection.[79,115] As the immune system is a major component of the cutaneous barrier, immune compromise could increase the risk for skin failure in conjunction with other conditions. For both chemotherapeutics and immunosuppressants, it is the compounded effects of both the condition and the treatment that predisposes the skin to fail.

THE DYING PROCESS

Skin disruption in persons who are dying was recognized the 19th Century when Charcot described the *Decubitus Ominosus*.[116] The dying process is known to be associated with alterations in skin integrity, and a variety of terminologies have been offered to describe these phenomena including Kennedy Terminal Ulcer (KTU), Trombley Brennan Terminal Tissue Injury (TBTTI), and Skin Changes at Life's End (SCALE).[1,11–13] In today's healthcare environment, incorporation of terminal ulcer terminology is problematic particularly when there is no common consensus as to the end-of-life period.[1,14] Medical technology offers powerful interventions to prolong or delay the dying process rendering terminal ulcer terminology inappropriate except in patients who are recognized by both clinicians and family as actively dying.[14]

Research on skin changes associated with the dying process is sparse, however commonly recognized physiological changes include hypotension and decreased oxygen saturation.[117,118] In an effort to define skin failure within this context, the proposed model connects a common denominator of physiologic principles to this clinical syndrome which is recognized across the healthcare continuum. The model therefore considers disruption of skin integrity related to the dying process as a component of the spectrum of skin failure.

DERMATOLOGIC DISORDERS AND MISCELLANEOUS CONDITIONS

The dermatologic literature offers several disorders postulated as causing skin failure.[8] These include graft vs. host disease, Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythroderma (exfoliative dermatitis) that are accompanied by hemodynamic changes, impaired thermoregulatory control, and metabolic complications.[8–10,119,120] Because their single organ genesis as proposed by the dermatologic discipline, they appear as a separate pathway in our model.

Other conditions such as radiation dermatitis can compromise the intrinsic structure of skin and underlying tissues rendering it prone to failure when subjected to internal and external stressors. The long-term histopathological effects of radiation therapy can remain for months or years depending on dose and volume irradiated. While these effects typically involve the epidermal and dermal layers, subcutaneous or other structures (subcutaneous fat, muscle, bone, blood vessels) can also be affected thus creating an increased vulnerability to skin failure.[121,122]

Scar tissue contains attenuated vasculature and densely packed collagen that maintains only 80% of strength of

normal tissue, which is attained one year after injury.[123] In addition, many closed pressure injuries might have ongoing activity in the proliferative and remodeling phases of wound healing, thereby resulting in intrinsic structural weakness.[124] As this represents structural compromise, scar tissue is a potential starting point for skin failure.

CONCLUSIONS

Skin is the largest organ of the body, and also the most complex. As there is no single function of skin, there is no single cause of skin failure. From a clinical standpoint, the term skin failure likely applies not only to skin but to levels of tissue adjacent and underneath. Clarification of the pathophysiology of skin failure has important implications for clinical care, quality measurement, and health care policy. In reviewing contributors to skin failure, several common pathophysiologic mechanisms emerge which can be considered a pathway toward this clinical phenomenon. This manuscript proposes a model that relies upon physiologic principles common to other organ systems that apply to patients across the healthcare continuum. It is likely that future research will reveal additional physiologic mechanisms that are equally if not more important to consider in this model such as mitochondrial dysfunction.[125,126]

When assessing a wound, the clinician must carefully evaluate the patient to determine the risk factors that exist and critically determine the most probable etiology. Documentation should include a full patient assessment that includes risk factors present and underlying illnesses. The term acute skin failure could be considered when causative factors are associated with acute critical illness. It should be cautioned that the terms skin failure and acute skin failure should not be applied to wounds because of inadequate or inconsistent prevention strategies. Proper prevention should always be applied based on a patient's risk factors. When it has been deemed that all possible strategies have been applied, including timely interventions and care plan revision, and a wound still evolves, the next step is to determine the primary etiology.

The proposed model for skin failure brings together a variety of factors that include an array of risk factors, pathophysiologic consequences, and overlapping nomenclatures that include terminal ulceration. The goal is to unify terminology and eliminate confusion in the regulatory arena. Given the controversies on classification and nomenclature discussed herein, researchers and clinicians require a path to further study skin failure and acute skin failure phenomena, develop algorithms and biologic markers to further clarify the diagnosis, and supply a clear rationale for adapting uniform and consistent language. Such a path can guide future investigations which will more clearly elucidate the concept of skin failure. Given the controversies discussed, we urge caution regarding assignment of an International Classification of Disease (ICD) code for skin failure or related components on the skin failure spectrum such as terminal ulceration until further data-driven evidence is obtained and interdisciplinary consensus is reached. A common understanding of skin failure could reveal new pathways for prevention, early intervention, and treatment. ●

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