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Revisiting the Pathophysiology of Acute Respiratory Distress Syndrome in Burn with Inhalation Injury: A Comprehensive Review

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ABSTRACT

Acute respiratory distress syndrome (ARDS) is a common complication in severe burn patients, arising from inflammatory responses following burns or inhalation injuries. This literature review explores the mechanisms and diagnostic approaches for ARDS in burn patients. Methods involved searching open-access journals using specific keywords on PubMed, Google Scholar, and Elsevier. The review highlights the involvement of various immune cells and cytokines in ARDS pathophysiology, with diagnostic tools including clinical signs, imaging, and bronchoscopy. Therapeutic strategies focus on ventilation and pharmacological interventions targeting inflammation. Further research is needed to better understand ARDS in burn patients, particularly regarding inflammatory markers and pharmacological treatments.

KEYWORDS: acute respiratory distress syndrome (ARDS), burn injury, inhalation injury, pathophysiology, inflammatory response, immune cells, cytokines, diagnostic modalities, ventilation therapy, pharmacological therapy

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a critical condition marked by inadequate oxygen levels and inflexible, non-compliant lungs. Acute respiratory distress syndrome is also identified by comparing the patient's partial oxygen pressure in arterial blood (PaO_2) with the fraction of the oxygen in the inspired air (FiO_2). This disorder related to damage to the capillary endothelium and widespread harm to the tiny air sacs in the lungs. When acute respiratory distress syndrome occurs, patients often experience different levels of narrowing of the pulmonary arteries and may encounter pulmonary hypertension.[1]

Acute respiratory distress syndrome is a common complication in severe burn patients, whether they have suffered inhalation injuries or not. In patients with cutaneous burns, acute respiratory distress syndrome is caused by the body's inflammatory response during the acute phase of the burn or the sepsis phase following the burn. On the other hand, the development of acute respiratory distress syndrome in patients with inhalation injuries is thought to be related to the circulation of the bronchi, the effects of Nitric Oxide (NO), and blockages in the respiratory tract.[2]

After breathing in smoke, substances are released, which block the airway passage. These substances consist of fibrin, neutrophils, mucus, and debris from epithelial cells. Blocked alveoli are not adequately ventilated, resulting in an elevated pulmonary shunt fraction that alters the ventilation-to-perfusion ratio. Meanwhile, open alveoli become overly inflated during mechanical ventilation, triggering the release of inflammatory cytokines from the alveolar wall and causing damage due to mechanical ventilation. These alterations diminish gas exchange, leading to low oxygen levels. Research indicates that inhalation injuries from smoke can impair gas exchange in animal models by increasing capillary permeability and promoting fluid movement across the alveolar epithelial-endothelial barrier.[3]

A prior study suggested that inhalation injury independently increases the risk of developing acute respiratory distress syndrome, but the severity of the injury, as assessed by a scoring system, did not contribute to the likelihood of acute respiratory distress syndrome development. The symptoms and outcomes of burn patients who develop acute respiratory

distress syndrome due to smoke inhalation may differ from those who develop acute respiratory distress syndrome due to cutaneous burns. Knowing the pathophysiology of acute respiratory distress syndrome in burn patients will affect the therapeutic management and prognosis.[4]

We compiled and analyzed information from numerous web databases, including open access journals relevant to the keywords “Acute Respiratory Distress Syndrome”, “Inhalation Injury”, and “ARDS in Inhalation Injury” from PubMed, Google Scholar, and Elsevier, collected, organized, and summarized the data into this literature review aiming to describe the pathophysiology and mechanism of acute respiratory distress syndrome in inhalation injury.

BURN INJURY AND INHALATION INJURY

Overview of Burn Injury

A burn injury occurs when the skin comes into contact with a source of heat. Various factors such as high temperature, electricity, friction, radiation, and chemicals can lead to burn injuries. The extent of burn injuries varies, and an increase in the body surface area affected by the burn injury influences both wound severity and patient mortality. Additionally, key factors that directly influence the severity of the injury include the burn's location, the temperature, and the duration of exposure to the heat source, with these factors often working together to worsen the injury.[5]

Burns can be classified as "partial-thickness" or "full-thickness". In cases of superficial partial-thickness burns where the damage is limited to the epidermis and the outer part of the dermis, with most appendage structures intact, the recovery is typically quick (within 10–14 days) and the risk of scarring is low. Conversely, if the burn extends into the deeper layers of the dermis, with more extensive damage to appendages, the regeneration of the epithelium will take longer (3–6 weeks) and there will be a high likelihood of hypertrophic scarring. Full-thickness burns involve the destruction of all skin layers and usually necessitate surgical intervention to ensure proper wound healing.[6]

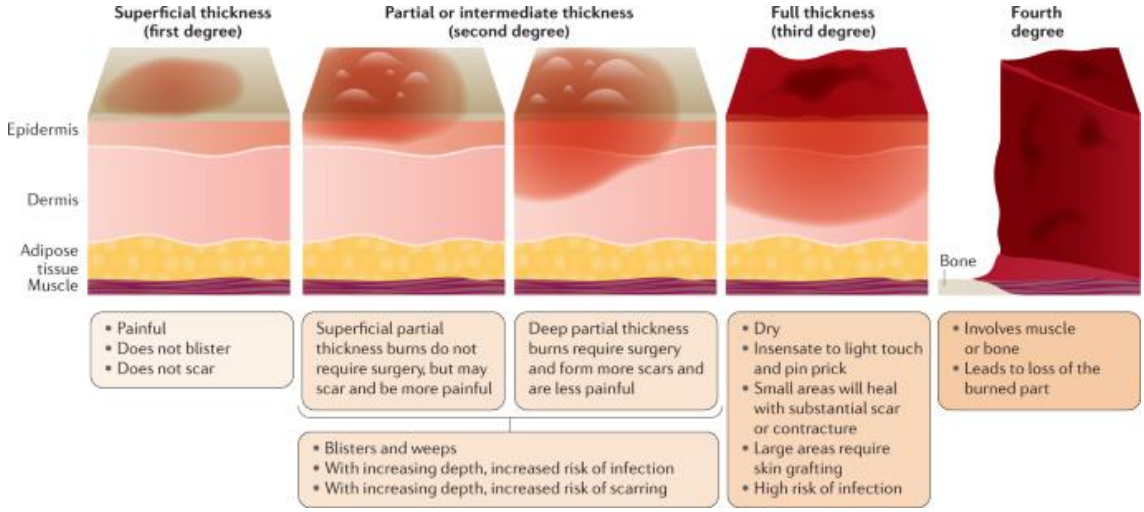

Figure 1. Classification of burn injuries according to the degree of depths.[7]

The damage caused by burns covering more than 30% of the total body surface area leads to significant loss of fluids in the body, as well as the production and release of inflammatory substances. This in turn triggers a systemic effect, specifically a distinct cardiovascular malfunction called burn shock. This is a complicated process that impairs both the circulatory system and the microcirculation, causing swelling in both the burned and unaffected areas. Even with immediate treatment and sufficient fluid support, this physiological condition cannot be reversed. Additionally, burn injuries also lead to the leakage of plasma from blood vessels, resulting in increased systemic vascular resistance and decreased blood flow in the extremities. These changes cause alterations in blood circulation, including a decrease in the heart pump capacity due to reduced plasma volume, as well as a decrease in urine output.[8]

Another response of the body to a burn is the development of swelling. Swelling occurs when the amount of fluid leaving the small blood vessels exceeds the amount entering them. The process of swelling occurs in two phases. The initial phase, which begins within the first hour after the burn, is due to a rapid increase in the water content of the damaged tissues. The second phase, occurring 12 to 24 hours after the burn, involves a slower, gradual increase in fluid accumulation in both the burned and healthy skin and soft tissues.[8]

Thermal injury and exposure to irritants in the upper respiratory tract lead to the release of inflammatory mediators and reactive oxygen species (ROS), increased permeability of blood vessels, and the formation of swelling. This swelling in the upper respiratory tract can progress to blockage of the airways and bronchospasm, reaching its peak at 24 hours. Additionally, within the first 24 hours, there may be bleeding, congestion of the mucous membranes, ulceration, and

laryngospasm. The damaged mucosal cells produce excessive exudates containing a high level of protein, inflammatory cells, and dead tissue.[9]

The release of these inflammatory mediators, such as interleukin-1α (IL-1 α), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor α (TNF-α), attracts neutrophils, which then move through the glandular epithelium and into the airway space. The resulting damage to the columnar epithelia inhibits the mucociliary system of the trachea, allowing material and bacteria from the upper airway to migrate distally, leading to blockage and potential infection. In severe burn cases, respiratory failure can occur, characterized by low oxygen levels and progressing to acute lung injury or acute respiratory distress syndrome (ARDS). ARDS is a major cause of mortality in burn patients.[10]

Inhalation Injury

Inhalation injury is found in about one-third of all burn cases, but it contributes to up to 90% of all burn-related deaths. In terms of anatomy, injuries are categorized into three groups: 1) Heat injury, confined to upper airway due to effective heat dissipation in the upper airway, the limited heat capacity of air, and the reflex closure of the larynx, injuries from extremely hot air typically affect only the airway structures above the carina. Damage to these structures can lead to significant swelling of the tongue, epiglottis, and aryepiglottic folds, potentially causing obstruction. 2) Local chemical irritation affecting the entire respiratory tract due to various materials are burned, they release harmful substances that can affect the respiratory system. These toxins from smoke can harm the cells lining the airway and the small blood vessels within it, 3) Systemic toxicity, such as from inhaling carbon monoxide or cyanide.[11]

The mechanism of damage can be categorized into four types: 1) injury to the upper airway, 2) injury to the lower airway, 3) injury to the lung tissue, and 4) systemic toxicity. Inhalation injuries lead to the formation of casts, a decrease in available surfactant, increased airway resistance, and reduced pulmonary compliance, resulting in acute lung injury and acute respiratory distress syndrome. The main pathophysiological changes in upper airway inhalation injury are caused by microvascular alterations due to direct thermal injury and chemical irritation. The heat alters proteins, triggering the complement cascade and the release of histamine. This is followed by the production of xanthine oxidase and the release of reactive oxygen species (ROS), which, in combination with nitric oxide in the endothelium, induces upper airway edema by raising microvascular pressure and local permeability.[12]

Injury to the lower airway results from the chemicals present in smoke. The air has a low heat capacity, and the bronchial circulation effectively regulates the temperature of the airway gases, such that most gases are at body temperature when passing through the glottis. Changes to the lung tissue occur gradually and depend on the severity of the injury and the patient's response. Damage to the lung tissue leads to an increase in the movement of fluid across the lung's blood vessels, which is directly related to the duration of exposure to smoke and toxins.[12]

This type of injury is marked by reduced protein permeability, heightened permeability to small particles, increased pressure in the pulmonary blood vessels, and a loss of hypoxic pulmonary vasoconstriction. The main pathological changes in inhalation injury include the development of edema, reduced lung compliance due to the presence of excess lung water and pulmonary lymph, and immediate inactivation of surfactant. Subsequently, there is a mismatch between ventilation and blood flow, leading to severe oxygen deficiency and acute respiratory distress syndrome (ARDS).[12]

PATHOPHYSIOLOGY OF ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Normal Pulmonary Physiology

Ventilation of the pulmonary functional unit happens through both convection and diffusion. During inhalation, the negative pressure in the chest cavity, created by the respiratory muscles, draws oxygen-rich air into the lungs. Upon exhalation, the passive recoil of the chest wall expels air depleted of oxygen but rich in carbon dioxide. Deeper in the lungs, as the peripheral airways are approached, convection becomes less significant, and oxygen now diffuses towards the periphery due to the oxygen pressure gradient resulting from the absorption of oxygen at the alveolar surface. The higher carbon dioxide pressure in the capillaries compared to the alveoli causes carbon dioxide to diffuse into the alveoli and then from the alveoli towards the proximal airways where convection begins.[13]

Gas exchange takes place in the respiratory zone of the lung, which encompasses the respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli. The alveolar septum, which has numerous capillaries and thin walls, facilitates gas exchange. Adjacent alveoli are connected via small openings known as pores of Kohn, allowing for collateral airflow and pressure equalization between alveoli. The control of alveolar opening and closing, to regulate ventilation, occurs at the alveolar duct.[14]

The alveolar septum contains type I pneumocytes that are thin and line the alveoli, and type II pneumocytes that secrete surfactant to decrease alveolar surface tension. Alveolar macrophages, also called dust cells, play an active role in defending against pathogens and irritants.[14]

Gas exchange in the alveoli primarily happens through diffusion. Gases must pass through alveolar surfactant, alveolar epithelium, basement membrane, and capillary endothelium when traveling from the alveoli to the capillary blood. Fick’s law of diffusion states that the diffusion of a gas across the alveolar membrane increases with increased

surface area of the membrane, increased alveolar pressure difference, increased gas solubility, and decreased membrane thickness.[14]

The exchange of both oxygen and carbon dioxide is perfusion limited, reaching equilibrium one-third of the way through the capillary/alveolar interface. Deoxygenated blood from the pulmonary arteries has a mixed venous oxygen tension (PVO_2) of 40 mmHg, and alveolar air has a partial pressure of oxygen in alveoli (PAO_2) of 100 mmHg, resulting in a movement of oxygen into capillaries until arterial blood equilibrates at 100 mmHg partial artial oxygen pressure (PaO_2). Meanwhile, carbon dioxide partial pressure ($PaCO_2$) decreases from a mixed venous carbon dioxide ($PVCO_2$) of 46 mmHg to a partial pressure of carbon dioxide ($PaCO_2$) of 40 mmHg in alveolar capillaries due to a partial pressure of carbon dioxide in alveoli ($PACO_2$) of 40 mmHg.[14]

The pulmonary epithelium is coated with lung surfactant, which plays a crucial role in regulating surface tension at the air-liquid interface during breathing. As air leaves the alveoli during expiration, their size reduces and surface area decreases. To prevent alveolar collapse, lung surfactant decreases surface tension to nearly zero at the end of expiration. This reduction in surface tension is achieved by enriching the surfactant film with surface-active components at the air-liquid interface, while the less surface-active components are excluded and stored in reservoirs below. Conversely, during inhalation, as the alveoli fill with air and their surface area increases, the surfactant film is quickly replenished with components from the reservoirs, causing the surface tension to return to equilibrium values.[15]

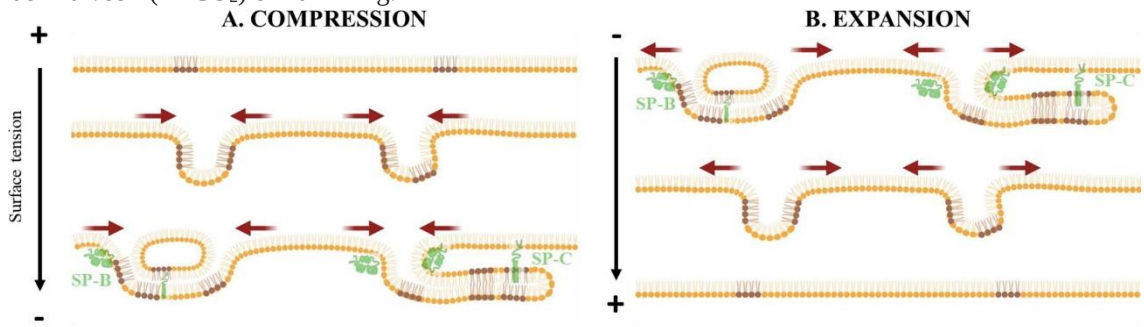

Figure 2. Compression (A) and expansion (B) of the lung surfactant film at the air–liquid interface. During compression (expiration), there is a re-arrangement of the components in the lung surfactant films: molecules with less surface activity (brown) are excluded from the interface, so that the surface is enriched in molecules with higher surface activitiy (orange). The reservoirs underneath the surface are stabilized by proteins surface B (SP-B) and proteins surface C (SP-C) (green). During expansion (inhalation), the less surface active components located underneath the interface spread again at the surface.[15]

Development of Acute Respiratory Distress Syndrome (ARDS) in Burn Patients

Following a burn injury, acute respiratory distress syndrome (ARDS) may develop as a result of direct lung damage from inhaled smoke and fumes, or it may be triggered by the inflammatory response linked to the burn or its infectious issues. The rise in capillary permeability in individuals with extensive burns is not limited to the site of the injury but also affects organs in other areas. This increase in vascular permeability results in fluid leakage into the interstitial space. In such situations, pulmonary edema is exacerbated by thermal injuries caused by inhaled smoke.[16]

Burns impact the immune system and cause tissue damage by releasing endogenous molecules known as damage-associated molecular patterns (DAMPs). These molecules originate from neutrophil cells or necrotic cells and include chromatin-associated high-mobility group box 1 protein (HMGb1), heat shock proteins (HSPs), purine metabolites like adenosine triphosphate (ATP), and uric acid. Damage-associated molecular patterns directly bind to immune cells via pattern recognition receptors (PRRs), such as toll-like receptors (TLRs) on the surface of antigen-presenting cells (APCs). The binding of damage-associated molecular patterns and toll-like receptors generates signals in cells, initiated by the formation of Myddosome, which consists of myeloid differentiation primary response gene 88 (MyD88) and interleukin-1 receptor-associated kinases (IRAKs).[17]

During the formation stage, interleukin-1 receptor-associated kinases 4 (IRAK4) undergoes auto-phosphorylation, phosphorylates and activates interleukin-1 receptor-associated kinases 1 (IRAK1), leading to IRAK1's release from the Myddosome complex and its association with tumor necrosis factor α receptor-associated factor 6 (TRAF6) to activate tumor growth factor-β-activated kinase (TAK1). Subsequently, tumor growth factor-β-activated kinase activates two distinct signaling pathways: the inhibitor of nuclear factor-κB kinase (IKK) complex-nucelar factor-κB pathway and the mitogen-activated protein kinase (MAPK) pathway. Tumor growth factor-β-activated kinase binds to the inhibitor of nuclear factor-κB kinase complex via the ubiquitin chain, inducing kappa kinase (IKK-β) inhibitor activity. Upon activation, inducing kappa kinase degrades the kappa inhibitor (IK-) β, leading to the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Tumor growth factor-β-activated kinase also activates mitogen-activated protein kinase (MAPK), which mediates

the activation of activator protein 1 (AP-1). The transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells and activator protein 1 (AP-1) translocate to the nucleus, inducing the expression of various genes encoding proinflammatory cytokines, such as tumor necrosis factor α, interleukin-1β, and interleukin-6.[17]

The production of proinflammatory mediators following a burn plays a key role in acute respiratory distress syndrome and the development of multiple organ failure. Research has shown that acute respiratory distress syndrome is a secondary outcome of cutaneous burn injury and is a process mediated by neutrophils. The heightened activation of the nuclear factor kappa-light-chain-enhancer of activated B cells pathway results in increased expression of interleukin-8 and intercellular adhesion molecule 1 (ICAM-1), which signal the recruitment and translocation of neutrophils into the pulmonary parenchyma. Once in the lungs, neutrophils cause damage by releasing granulated contents and generating reactive oxygen species.[18]

Role of Inhalation Injury

The substances burning of inhalation injury influenced by the smoke and the intensity of the body's inflammatory responses, leading to a strong reaction from the lung tissue. The main pathological changes below the vocal cords following inhalation injury include increased blood flow to the airway lining, constriction of the air passages, and the creation of solidified material from the excessive discharge of fibrin into the air passages. This also causes the shedding of the airway lining, thickened mucus, and impairment of both the surfactant and the mucociliary escalator function.[19]

Initially, exposure to chemical irritants and smoke in the lungs triggers the production of neuropeptides, leading to a significant inflammatory reaction. This reaction involves the activation of sensory C-fibers in the vagal nerve, which contain pro-inflammatory peptides, neurokinins, and calcitonin gene-related peptide. Neural endopeptidase plays a crucial role in altering these neuropeptides, leading to bronchoconstriction and the activation of inducible nitric oxide synthase (iNOS), which produces reactive oxygen species and inhibits hypoxic pulmonary vasoconstriction. The main factor contributing to pathological changes is the increased blood flow in the airways. Dysregulation of hypoxic pulmonary vasoconstriction causes a shift of deoxygenated blood from the right to the left side of the heart, resulting in systemic hypoxemia. Irritation also causes bronchospasm and disrupts gas exchange in the distal airways. Edema is a secondary consequence of the inflammatory cascade, leading to small airway blockages, compromised ventilation, and ultimately, impaired oxygenation. These pathologies result in ventilation/perfusion (V/Q) mismatching, intrapulmonary shunting, and decreased oxygenation.[19]

The cause of bronchospasm following inhalation injury is not fully understood, but it may result from the release of neuropeptides produced in the lining below the airway. The extent of constriction depends on the substances in the inhaled smoke and the individual airway's sensitivity to the chemical irritants and toxins. The bronchospasm worsens the narrowing of the small airways triggered by increased blood flow to the airway lining. This effect is heightened by the impaired surfactant function, which leads to the collapse of the air sacs and atelectasis.[19]

Ultimately, narrowed airways become blocked by formations known as airway casts. These casts develop from blood clots, mucus, and sloughed pulmonary epithelium that cannot be expelled due to impaired mucociliary escalator function. They stick to the airway walls, reducing the space inside the airway and affecting ventilation. Additionally, these casts can obstruct endotracheal tubes. Gravity causes the casts to move toward the lower airways, and when combined with impaired ciliary function, this leads to reduced ventilation of the air sacs and shunting, ultimately resulting in systemic hypoxia.[19]

Moreover, the increased blood flow to the bronchial tubes and consequently to the bronchial mucus glands stimulates the production of mucus. When excessive mucus is present and the ciliary function is impaired, it leads to the formation of obstructive airway casts, which can have harmful effects. Airway obstruction poses a life-threatening risk, and even the blockage of certain proximal bronchi can lead to reduced ventilation of an entire section of the lungs. Additionally, the loss of the epithelial integrity and impaired cell function in the airway reduces the clearance of bacteria, either through ciliary dysfunction or impaired phagocytosis. These factors elevate the risk of developing an airway or lung infection. Failing to expel casts and secretions after an inhalation injury can be perilous and fatal by compromising ventilation and causing shunting that impairs oxygenation.[19]

Inflammatory substances (such as cytokines and products of the coagulation system) are believed to cause changes characteristic of acute respiratory distress syndrome. The acute phase of acute respiratory distress syndrome is marked by the influx of protein-rich edema fluid into air spaces due to increased permeability of the alveolar-capillary barrier and endothelial injury. Interestingly, it has been shown that the severity of inhalation injury does not necessarily correspond to the development of acute respiratory distress syndrome in burned patients. While the damage from smoke inhalation starts closer to the airways and decreases in impact as it moves deeper into the lung, the damage in acute respiratory distress syndrome begins farther in the alveoli and lessens as it progresses toward the airways. Smoke inhalation and acute respiratory distress syndrome are two separate but interconnected conditions.[19]

CELLULAR AND MOLECULAR MECHANISMS

Inflammatory Mediators

At the location of the burn injury, the primary tissue is damaged due to the breakdown of proteins, leading to the release of harmful proinflammatory substances and factors that activate platelets into the bloodstream. Cells of the immune system, like macrophages and neutrophils, generate oxygen free radicals to eliminate pathogens, which in turn harm the skin structures, causing a robust immune response known as systemic inflammatory response syndrome (SIRS). The innate immune system provides rapid and nonspecific defenses against infections, recognizing specific patterns associated with microbial pathogens (PAMPs) and damage (DAMPs) through pattern recognition receptors (PRRs), which encompass various classes such as toll-like receptors (TLR), nucleotide-binding and oligomerization domain like receptors (NLR), retinoic acid-inducible gene I like receptors (RLR), and C-type lectin receptors (CLR).[20]

Outside the body, epithelial cells produce defensins, lysozymes, and cathelicidins to destroy pathogen cell walls and exhibit antibacterial properties. Inside the body, the innate immune system comprises macrophages, neutrophils, dendritic cells (DC), and others, providing a rapid and nonspecific response to well-known antigens. When these fragments bind to toll-like receptors on the surface of immune cells, the pre-programmed cells are activated. Toll-like receptors also recognize common antigenic molecules from different types of bacteria. The binding of patterns associated with microbial pathogens to toll-like receptors triggers the swift engulfing of suspicious pathogens. Furthermore, innate immunity involves the mobilization of non-cellular defense mechanisms, such as complement, coagulation, and proinflammatory cytokines, which bolster the acquired immune system.[20]

A burn injury results in an increase in the quantity of mast cells in the affected tissues, leading to their activation and the release of substances like histamine, heparin, and enzymes such as chymase, cathepsin G, and hydroxypeptidase A. These substances, when released by mast cells, support the healing of wounds, including those caused by burns. Following a burn injury, mast cells undergo atrophy, and as a result, significantly higher levels of mast cells are present in the scar tissue, indicating their role in facilitating wound healing. In fact, the levels of mast cells in burn scar tissue can be 10–100 times higher than in healthy skin. Studies using rodent models have shown that elevated levels of mast cells can persist for up to 30 days after a burn.[20]

The recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) stimulates the production of cytokines and chemokines by monocytes. Specific chemoattractants, including interleukin-6, interleukin-8, interleukin-8β, adenosine, and the lymphocyte function-associated antigen-1 (LFA-1) complex, are associated with monocyte migration to burn sites. Burns lead to an increase in the number of monocytes in the blood. Studies have revealed that burn patients have fewer monocytes expressing the human leukocyte antigen (HLA-DR), and this number is further reduced in patients with burn-related sepsis. Monocytes exit the bloodstream to reach affected tissues, where they transform into tissue macrophages.[20]

Severe burns not only cause inflammation but also induce metabolic changes. When uncontrolled, these changes can lead to severe metabolic dysfunction, triggering the stimulation of the nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP-3) inflammasome. Additionally, NLRP3 can detect damage-associated molecular patterns (DAMPs) released after burn injuries. An hour after the burn, a decrease in NLRP3 expression was observed, resulting in reduced expression of factors involved in the wound healing process. The diminished production of proinflammatory cytokines and chemokines not only hinders keratinocyte migration and proliferation but also impairs immune cell chemotaxis.[20]

Natural killer (NK) and natural killer T (NKT) cells release cytotoxic granules that bind to infected cells and trigger apoptosis. The activation of natural killer cells by type I interferons leads to the synthesis of type II interferons, such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), perforin, granzymes, and antigen presentation. These cells express various receptors, including NCRs (natural cytotoxicity receptors) from the immunoglobulin family, KIRs (killer cell immunoglobulin-like receptors) that interact with class I major histocompatibility complex (MHC) molecules to transmit signals that either activate or inhibit cell activity, lectin-like receptors that play a role in activating or inhibiting natural killer cells, as well as natural killer cell activating receptors (such as natural cytotoxicity receptor [NCR], killer activation receptors [KAR], natural killer group [NKG-] 2D, NKG-C, NKG-E, Ly49D, -H, -P, -W) and NK cell activity inhibitory receptors (Ly49A, -B, -C, -E, -F, -G, Ly491, NKG2A, -B, interleukin-T2). Notably, natural cytotoxicity receptors encompass key receptors like natural kller group 2D, which is not exclusive to natural killer cell expression and is involved in recognizing damaged or transformed cells, as well as in Pseudomonas clearance.[20]

Excessive immune activation has the potential to trigger systemic inflammatory response syndrome (SIRS), resulting in remote tissue damage and the dysfunction of multiple organs, which greatly increases the risk of death. When pro-inflammatory cytokines, generated during the local immune response to facilitate the vascular permeability necessary for immune cell infiltration, enter the bloodstream, they can compromise the integrity of distant blood vessels, leading to organ failure as blood floods end organs. Within a few hours, the heightened capillary permeability can cause hypovolemic shock due to substantial fluid loss, necessitating immediate fluid resuscitation to prevent fatality. Following severe burns,

intestinal permeability may itself be the source of the inflammatory signaling responsible for distant tissue damage.[21]

Excessive neutrophilic inflammation is an early indicator of systemic inflammatory response syndrome, while macrophages play a significant role during the initial phase of the inflammatory response, notably through the production of pro-inflammatory cytokines like tumor necrosis factor α and interleukin-6. Elevated systemic levels of interleukin-6, interleukin-8, reactive nitrogen intermediates, and prostaglandins are detected in burn patients, all of which contribute to tissue damage both locally and at distant sites. interleukin-6 has been observed to be rapidly upregulated in the plasma of burn patients, reaching its peak within 6 hours post-burn. Furthermore, the levels of interleukin-6 have been found to be proportionate to the severity of the burn, and persistently high levels of interleukin-6 following a burn injury may indicate both the severity of the burn and the likelihood of mortality.[21]

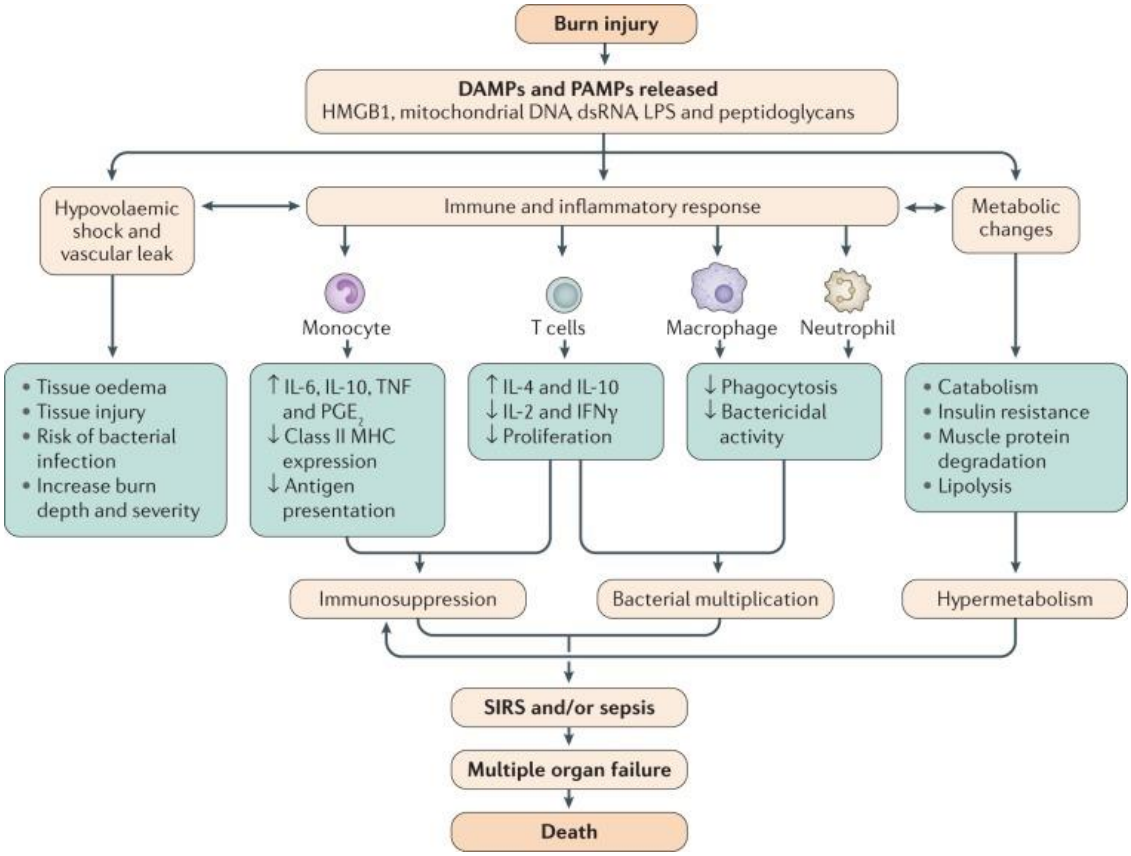

Figure 3. Tissue injury following severe burns results in release of endogenous damage-associated molecular patterns (DAMPs) such as mitochondrial DNA and double-stranded RNA (dsRNA), which along with exogenous pathogen-associated molecular pattern molecules (PAMPs) such as lipopolysaccharides (LPS) and peptidoglycans, can induce vascular leak, an inflammatory response and metabolic changes. Vascular leak and transfer of intravascular fluid to third spaces leads to tissue edema and further injury. The inflammatory response can result in immunosuppression and ineffective response to bacterial invasion. Metabolic changes include increased muscle protein degradation, insulin resistance and increased cardiac load. The culmination of these events is often systemic inflammatory response syndrome (SIRS), an inflammatory state affecting the whole body, which can lead to multiple organ failure, and ultimately, death. MHC, major histocompatibility complex; PGE2, prostaglandin E2; TNF, tumour necrosis factor. This mechanism of SIRS including the destruction of endothelial cells in pulmonary system with or wothout inhalation injury.[17]

Apoptosis and Cell Death

Neutrophils are the first leukocytes to respond to tissue damage and are recruited from the surrounding microvasculature via up regulation of P-selectin on the surface of vascular endothelial cells and circulating platelets. P-selectin binds to the surface of neutrophils, allowing them to tether and roll along the vascular endothelium before undergoing diapedesis and entering the inflamed tissues. Neutrophils use phagolysosomes, digestive vesicles formed by the fusion of a phagosome and a lysosome, to neutralize bacteria, resulting in the subsequent release of free radicals, such as reactive oxygen species, into the environment, which tend to also damage otherwise healthy cells near the site of injury. Neutrophils have also been shown to kill invading microbes by trapping them in extruded extracellular nets of histones and deoxyribonucleic acid (DNA). This programmed process called neutrophil extracellular traps (NETosis), frequently leading to cell death, can be activated

by microbes or their components as well as by cytokines and chemokines. Interestingly, formation of extracellular traps is not a unique feature of neutrophils as also basophils, eosinophils and mast cells as well as monocytes and macrophages can undergo a similar type of programmed response.[22]

Monocytes are the precursors to macrophages and both populations of phagocytes play important roles in immune function regulation, clearance of cellular debris, and tissue repair. Following their activation, these leukocytes transiently maintain their morphology as monocytes while secreting pro-inflammatory and angiogenic factors (e.g., interleukin-8, interleukin-1β, and tumor necrosis factor α) before differentiating into macrophages. Given the important regulatory role of the macrophage as a gatekeeper for providing an environment supportive or destructive for tissue healing.[22]

Mast cells are immune cells that reside in the dermal layer of the skin, promote acute inflammation, stimulate re-epithelialization and angiogenesis, and have been shown to play an important role in skin scarring. Thermal injuries cause the degranulation of resident mast cells which in turn results in the release of histamine, tumor necrosis factor α, prostaglandins, interleukin-1, and interleukin-6. These cytokines lead to increased vascular permeability thereby promoting and aiding in the recruitment of neutrophils and monocytes to the site of injury. The release of histamine ultimately leads to an uptick in the production of reactive oxygen species and triggers a rapid exocytosis of P-selectin that is a protein produced by activated platelets and endothelial cells. Similarly, the release of tumor necrosis factor α by mast cells upregulates the expression of E-Selectin, a receptor produced by endothelial cells. Both P- and E-Selectin are responsible for improved adhesion of leukocytes to the luminal surface of the vascular endothelial cells, thereby aiding in migration to the site of injury.[22]

Natural killer (NK) cells are innate lymphocytes of the dermis important to pathogen destruction and the early immune response. Natural killer cells have a reciprocally regulatory relationship with dendritic cells resulting in a unique and potent crosstalk of activation responsible for antibacterial defenses. Dendritic cells are phagocytic and antigen-presenting dermal leukocytes which serve as "immune sentinels" for T-cells while also augmenting the early immune response and clearing cellular debris. It has been proposed that dendritic cells sense dermal injuries via host-derived nucleic acids via toll-like receptors 7 and 9 and that this is the process through which they are recruited to the site of injury. Like macrophages, dendritic cells are responsible for phagocytosis of damaged tissue at the injury site. They have also been shown to play a role in wound repair.[22]

T-cells are the primary lymphocyte of the cell-mediated immune response; they are responsible for augmentation of the innate immune system and direct defense against foreign antigens. Compared to most other tissues, healthy skin and epithelium are unique in that they have a predominately Gamma-Delta (γδ) T-cell subpopulation, which has been shown to be pro-regenerative and plays a key role in regulation of infiltration, inflammation, and healing of burn wounds. Furthermore, it has been shown that this subset of T-cells regulates the infiltration of both myeloid cells and Alpha-Beta (αß) T-cells to the wound site during the acute stages of wound healing, before aiding in the transition from the inflammatory phase to the proliferative phase of wound healing.[22]

Naive T-cells can differentiate into T helper 1 (Th1) or T helper 2 (Th2) cells. T helper 1 cells are generally associated with a pro-inflammatory state and secrete interleukin-2 and interferon-γ (IFNγ) following their activation and differentiation. The Th2 phenotype, on the other hand, secretes cytokines that promote apoptosis, and an anti-inflammatory response including interleukin-4, interleukin-5, and interleukin-10, which in turn prompts B-cells to produce antibodies. In addition to the aforementioned cytokines, interleukin-4 and interleukin-5, B-cells have been shown to initiate immunoglobulin or antibody production in response to interleukin-15 which is secreted by dendritic cells, monocytes and macrophages, and endothelial cells. However, in the context of burn injuries, both local and systemic immunoglobulin or antibody levels have been shown to be significantly decreased during the first 48 hours following burn injuries with serum levels remaining low for weeks in some patients.[22]

Tissue repair involves a variety of mechanisms including edema reabsorption, resolution of inflammation and cell proliferation in order to repopulate the alveolar epithelium. Lung edema clearance is a crucial step. It has been documented that mild alveolar injury results in increased alveolar fluid reabsorption. However, in severe cases, the injured pneumocytes cannot sustain the active transport of ions and water across the epithelium. Therefore, cell integrity is essential for edema clearance. Regulation of the inflammatory response is a complex mechanism that requires interplay between several immune mediators.[23]

Apoptosis of inflammatory cells (mainly neutrophils) has also been documented when pro-survival signals, such as granulocyte-colony stimulating factor (G-CSF), disappear. Alveolar macrophages also play a role in this phase engulfing death cells. Finally, the regeneration of the alveolar structure requires the proliferation and differentiation of some progenitors into type I pneumocytes. Different growth factors (e.g. epidermic [EGF], keratinocyte [KGF] or hepatic growth factor [HGF]), acting through tyrosinkinase receptors, promote cell proliferation. Regarding the first, type II pneumocytes proliferate after injury and can originate type I cells. In addition, other cell types may also play a role in alveolar regeneration. Lung mesenchymal cells are activated after injury and, in addition to collagen synthesis, they may

secrete growth factors and even modulate the immune response by secreting anti-inflammatory cytokines.[23]

DIAGNOSTIC MODALITY

Clinical Assessment

History and clinical presentation are the most reliable methods of evaluation. Burns occurring in a closed space, burns around the nose and mouth, singed nasal hair, soot in the airway, carbonaceous sputum, hoarseness, wheezing, and stridor all suggest inhalation injury. A history of confusion, reduced level of consciousness or unconsciousness, and/or entrapment in a burning location, and carboxyhaemoglobin level >10% are additional indicators. Symptoms can be present on hospital admission or develop up to 48 hours post-burn, and they include dyspnoea, evidence of increased work of breathing, hoarseness, wheeze, stridor and ronchi, productive cough and soot stained/carbonaceous sputum. Bronchoscopic examination will often reveal carbonaceous debris, ulceration, pallor, and mucosal slough, although patients inhaling fine-particle smoke or burning hydrocarbons may have deceptively unremarkable bronchoscopy.[24]

Clinical manifestations of acute respiratory distress syndrome include pulmonary edema, inability to ventilate and eliminate carbon dioxide, and marked and severe arterial hypoxemia. If the patient is conscious and not intubated, tachypnea and dyspnea will be prominent. As per the American-European Consensus Conference, the diagnostic criterion was a ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) ratio ≤200 mmHg. The newer Berlin definition characterizes acute respiratory distress syndrome as acute, within one week of a clinical event not explained by cardiac failure, or fluid overload and associated with a positive end-expiratory pressure of ≥ 5 cmH_20. Acute respiratory distress syndrome is categorized as mild with a partial pressure to fractional inspired oxygen (PaO_2/FiO_2) between 200–300, moderate between 100–200, and severe below 100.[19]

Respiratory failure in the burn victim is often characterized by hypoxemia with evolution to acute lung injury or acute respiratory distress syndrome (ARDS). Even in patients without defined inhalation injury, the presence of acute respiratory distress syndrome is associated with poorer outcome. While many techniques have been developed to manage cutaneous injury, relatively few diagnosis-specific therapies have been identified for the patient with inhalation injury. A variety of factors explain slower progress for improvement in management of inhalation injury. In addition to smoke inhalation, the critically ill burn patient often has multiple mechanisms contributing to lung injury, such as sepsis, ventilator-induced lung injury, or systemic inflammation in response to burns. Thus, inhalation injury impacts burn patient outcome but its role is difficult to separate from the contributions of other injury drivers which affect the lungs.[25]

Imaging Techniques

In the definition of American-European Consensus Conference (AECC), bilateral infiltrates on frontal chest radiograph is one of the critical criteria. This criterion is detailed in the Berlin definition that bilateral infiltrates involving two or more quadrants on a frontal chest x-ray (CXR) should be considered. Some advantages of CXR should be emphasized, e.g., inexpensive, portable, sensitive for detection of pneumothorax and available to monitor devices' position, but limitations like relatively low quality, challenging for differential diagnosis should also be noticed. A daily routine CXR was recommended by the American College of Radiology in 2006. It is usually obtained in an anteroposterior projection. The radiographic manifestation evolves with the corresponding pathophysiological phases.[26] In the early time of the disease, usually in 48 hours, there is possible that no manifestations can be found in chest radiograph. In days 2–7 after the disease onset, the early patchy air-space infiltrates progress to bilateral consolidations. The pulmonary infiltrates usually involve more than three lobes. In severe cases, a "white lung" may be presented. In the late phase of the disease, fibrotic imaging signs can appear and sometimes result in the decreased irreversible respiratory function.[26]

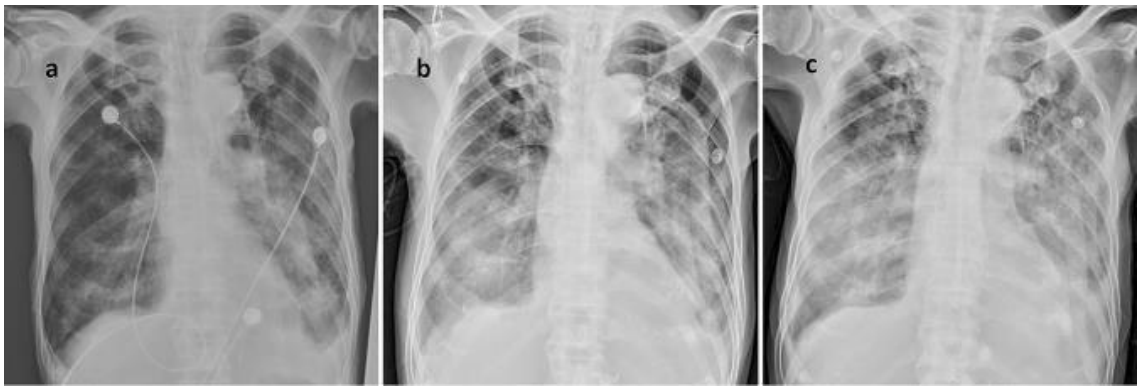

Figure 4. a) The baseline image within 24 hours of patient admission, demonstrating bilateral infiltrates. **b**) and **c**) 5 and 9 days after the admission, showing progression of the infiltration.[26]

Alveoli collapse and pulmonary interstitial edema cause main findings on computed tomography (CT) images. The CT manifestations evolve in the course of the disease. The most common findings are bilateral ground-glass opacities and consolidation that cannot fully be explained by cardiovascular factors or fluid overload, usually in dorsal dependent regions. In the late phase, signs of pulmonary fibrosis can be presented. Additional pathological findings, including pleural effusions, mediastinal lymphadenopathy, pneumothorax can also be shown on CT images and relatively measured. Besides, CT examination helps to confirm predisposing intrapulmonary or extrapulmonary factors. In a study comparing the CT appearance between intrapulmonary and extrapulmonary injury, the extent of the non-dependent region of intense parenchymal opacification was larger in patients with intrapulmonary injury than extrapulmonary injury.[26]

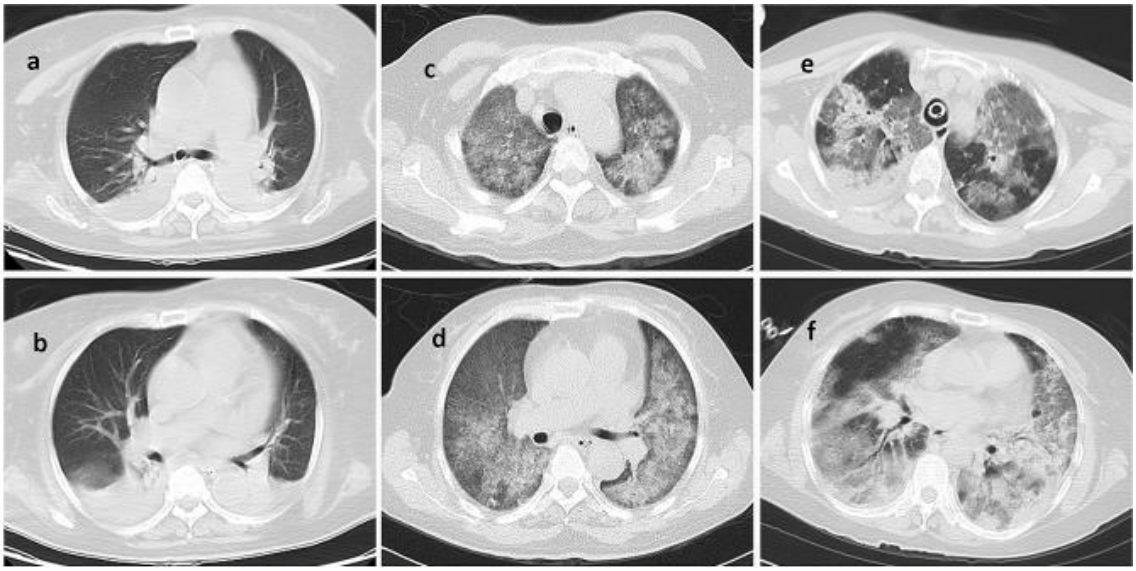

Figure 5. Typical images of chest CT of acute respiratory distress syndrome patients. Three patterns of acute respiratory distress syndrome on CT images. a, b Focal, c, d diffuse, e, f patchy.[26]

Accurate assessment of the severity of a burn injury, especially with lung involvement, is paramount because it forms the basis for all subsequent treatment decisions, triage plans and assessment of medical futility. Whenever possible, decisions about how to proceed after diagnosis and screening should incorporate patient preferences and expectations about quality of life. The critically ill burn patient has multiple mechanisms in addition to smoke inhalation that may contribute to lung injury such as sepsis, Ventilator-Induced Lung Injury (VILI) or a systemic inflammation in response to burns. Thus, inhalation injury has a significant effect on burn patient outcome but is difficult to separate from the contribution of other mechanisms which also affect the lungs.[25]

THERAPEUTIC APPROACHES

Mechanical Ventilation Strategies

The standard approach to protective mechanical ventilation (PMV) includes small tidal volumes (TVs) to limit volutrauma, setting positive end-expiratory pressure (PEEP) to minimize atelectrauma, and recruitment maneuvers (RMs) to open collapsed regions of the lung. An individualized approach to mechanical ventilation (MV) based on lung pathophysiology and morphology, acute respiratory distress syndrome cause, and lung imaging and monitoring has been suggested to improve ventilation practice and outcome. In addition, protective mechanical ventilation has been expanded beyond the lung itself to include right-heart-protective ventilation, diaphragmatic-protective ventilation, minimization of repetitive-stress injury, capillary-stress reduction, and consideration of patient self-inflicted lung injury (P-SILI).[27]

A tidal volume of 4 to 6 mL/kg predicted body weight is commonly used to maintain a plateau pressure (Pplat) < 30 cm h 2 o.14 Minimizing airway driving pressure (DP), calculated as Pplat minus positive end-expiratory pressure (PEEP), is another suggested strategy for selecting tidal volume. Importantly, plateau pressure and driving pressure are indirect measures for peak lung stress. When functional residual capacity is markedly reduced in severe acute respiratory distress syndrome, overdistention can occur in nondependent regions despite achieving target levels.[27]

Unique characteristics of burn patients may affect the successful application of a low tidal volume (TV) approach. For example, low tidal volume in a burn patient with poor chest compliance and/or inhalation injury with obstruction of the conducting airways can result in lung underinflation. A retrospective study in pediatric burn patients with inhalation injury found that a low tidal volume approach was associated with more atelectasis, longer duration of mechanical

ventilation, and a higher incidence of acute respiratory distress syndrome than a higher tidal volume approach.[27]

Positive end-expiratory pressure (PEEP) is used in acute respiratory distress syndrome to minimize atelectasis and reduce lung heterogeneity, thereby increasing the amount of aerated lung available for ventilation. Positive end-expiratory pressure may also shift edema fluid from the flooded alveoli into the interstitial space, decreasing shunt fraction and promoting more uniform alveolar mechanics. However, positive end-expiratory pressure will only have benefit when alveolar recruitment surpasses overexpansion of patent alveoli. There is no simple method to assess the risk-to-benefit ratio of different positive end-expiratory pressure levels. In acute respiratory distress syndrome, derecruitment is a continuous process in which the rate of collapse increases as positive end-expiratory pressure decreases. With decreasing levels of positive end-expiratory pressure, derecruitment ceases in the sternal lung zones at positive end-expiratory pressure of 10 cm H_2O, whereas it continues in dorsal regions down to 0 cm H_2O. Consequently, a minimum positive end-expiratory pressure of 10 to 12 cm H_2O might reduce derecruitment during the acute phase of acute respiratory distress syndrome, and higher levels may be necessary in severe cases. Approaches to select an optimal positive end-expiratory pressure level in acute respiratory distress syndrome include the use of tables that assign positive end-expiratory pressure based on the fraction of the oxygen in the inspired air (FiO_2), use of the highest positive end-expiratory pressure that optimizes oxygenation while allowing an acceptable tidal volume and plateau pressure, and bedside positive end-expiratory pressure titration based on lung compliance and recruitability.[27]

In acute respiratory distress syndrome, right ventricle (RV) dysfunction can lead to right ventricle failure (acute cor pulmonale), and if left untreated, cardiogenic shock can develop. Elevated right-heart pressure can also worsen hypoxemia by right-to-left intracardiac shunting of deoxygenated blood through a patent foramen ovale. Right ventricle protective mechanical ventilation has been suggested to reduce right ventricle afterload to include: (1) minimized lung stress by limiting plateau pressure and driving pressure, (2) reduced pulmonary vasoconstriction by improving oxygenation and control of carbon dioxyde (CO_2), and (3) prone positioning to unload the right ventricle. Optimization of right ventricle protective positive end-expiratory pressure must balance alveolar recruitment and overdistention. If right ventricle protective measures are insufficient (or unfeasible), ancillary therapies, such as inhaled vasodilators or extracorporeal membrane oxygenation (ECMO), may be required.[27]

Higher ventilatory frequencies are often used with low tidal volume ventilation to reduce hypercapnia, but this may have detrimental effects on respiratory mechanics, gas exchange, and cumulative lung trauma. Higher ventilatory frequencies shorten inspiratory time, resulting in the need for higher peak-flow rates, which may augment parenchymal shear stress, worsen oxygenation, and contribute to greater pressure-related cyclic lung stress and strain. Shortened expiration times may have detrimental effects, including dynamic hyperinflation, reduced compliance, increased total pulmonary pressure (TPP), and diaphragmatic dysfunction. A reduction of the frequency of ventilation with resulting hypercapnia may be beneficial in acute respiratory distress syndrome by facilitating a reduction of the cumulative intensity of cyclic stress and strain.[27]

Pharmacological Interventions

There is no specific therapy that targets inhalational injury; however, there are a range of supportive interventions, based on biological plausibility, that are potentially suitable to treat the physiologic perturbations associated with smoke inhalation acute respiratory distress syndrome. Hypoxia-inducible factor (HIF) is a heterodimeric protein involved in various essential pathways, including metabolic reprogramming, immune modulation, angiogenesis and cell cycle regulation. Hypoxia-inducible factor is routinely degraded in homeostasis conditions via the prolyl hydroxylase domain/von Hippel–Lindau protein pathway. However, hypoxia-inducible factor is stabilized in acute respiratory distress syndrome via various mechanisms (oxygen-dependent and independent) as an endogenous protective pathway and plays multifaceted roles in different cell populations.[28]

There are many drugs for the treatment of acute respiratory distress syndrome currently in the experimental or clinical stages of development. One of these drugs is aspirin, an antiplatelet and anti-inflammatory agent that showed potential in preclinical and observational clinical studies for the prevention and treatment of acute respiratory distress syndrome. However, aspirin was reported to have no benefit in preventing acute respiratory distress syndrome in a randomized study of 390 at-risk patients.[29]

Although there are studies on granulocyte–monocyte colony stimulating factor (GM-CSF), it has not been adopted as routine therapy for adults with acute respiratory distress syndrome due to insufficient evidence. Granulocyte–monocyte colony stimulating factor plays an important role in the repair of injured lung and in the enhancement of alveolar macrophage function. Preclinical studies have suggested that bronchoalveolar lavage with granulocyte–monocyte colony stimulating factor is associated with improved survival in patients with acute respiratory distress syndrome.[29]

Experimental studies have been conducted in an effort to determine whether certain therapies are beneficial in acute respiratory distress syndrome. One of these is stem cell therapy. Preclinical studies have demonstrated that exogenous mesenchymal stem cell (MSC) therapy may

mitigate lung injury and support repair. In animal studies, mesenchymal stem cell were found to secrete growth factors and cytokines that can modulate local inflammation and support tissue repair, improve bacterial clearance, and potentially differentiate into mature cells to replace the injured cells.[29]

Bosentan is used in the treatment of diseases, such as pulmonary hypertension due to its effect on vascular structures, and also exerts an anti-inflammatory effect via endothelin 1 (ET-1). Under normal physiological conditions, endothelin 1 binds to the endothelin type B receptor in endothelial cells, allowing the production of nitric oxide (NO) and prostacyclin. Moreover, it induces cytokine, growth factor, collagen, and aldosterone production, thus leading to proinflammatory effects. It also affects inflammation through leukocyte–endothelium interactions mediated by the upregulation of P selectin by endothelin 1. In addition, it is believed that endothelin 1 has important proinflammatory activity in the airways via granulocyte–monocyte colony stimulating factor through chemoattractant agents, such as interleukin-6 or interleukin-8. Transforming growth factor-β induces the secretion of endothelin 1, which has many proinflammatory effects, including fibroblast migration.[29]

Proteasome inhibitors such as bortezomib and carfilzomib were inhibiting the proteasome may induce anti-inflammatory effects. Hypoxia-inducible factor 1 (HIF-1α), a transcription factor that controls expression of numerous genes, is targeted for ubiquitin proteasomal degradation. HIF-1α appears to be protective from acute respiratory distress syndrome as pharmacologic stabilization of HIF-1α lessens acute lung injury (ALI) severity in preclinical models. Inhibiting the pro-inflammatory protein, F-box protein 3 (Fbxo3), effectively lessens the severity of viral pneumonia, septic shock, cytokine-driven systemic inflammation and acute respiratory distress syndrome in preclinical models, underscoring potential for targeting of the ubiquitin proteasome system in acute respiratory distress syndrome.[30]

Currently untested alternatives for the treatment and prevention of acute respiratory distress syndrome in human randomized controlled trials (RCT) are inhaled corticosteroids, angiotensin converting enzyme (ACE) inhibitors, and peroxisome proliferator receptor (PPAR) agonists. Animal data suggests that nebulized corticosteroids improve dynamic lung compliance and oxygenation, and decrease lung inflammation in sepsis-induced acute respiratory distress syndrome models. Angiotensin II induces nuclear factor kappa-light-chain-enhancer of activated B cells gene expression, hence, blocking the renin-angiotensin axis may be beneficial to acute respiratory distress syndrome patients based on animal data and an observational human study. On the other hand, PPARs and their respective ligands negatively control pro-inflammatory gene expression. Their agonists reduce inflammation and vascular leakage in animal acute respiratory distress syndrome experimental models. However, human RCTs are necessary to examine the effect and efficiency of all these modalities.[30]

CHALLENGES AND FUTURE DIRECTIONS

The understanding on pathophysiology of acute respiratory distress syndrome (ARDS) in burn injury still need some research. The chemokine and cytokine that important playing the role in burn injury itself or inhalation injury should be explored more. This is necessary to take one-step forward for early diagnostic and management of acute respiratory distress syndrome related in burn patients. The diagnostic tools such as computed tomography scan and chest X-ray showing good sensitivity but another diagnostic approach should be considered to differentiate with another lung injury. We need more research about the marker that significantly increased in acute respiratory distress syndrome with burn injury. The bronchoscopy might seem effective but not efficient enough to diagnostic and beginning of therapeutical approach. Surely, the research about effectiveness of currently therapeutic approach for acute respiratory distress syndrome in burn injury still lacks since there are some research have different outcomes for ventilation therapy. The pharmacological approach also did not have any specific evidence for being used in acute respiratory distress syndrome patient related to burn injury.

CONCLUSION

The pathophysiology of acute respiratory distress syndrome (ARDS) in burn patient is a complex interactions of immunity. There are many chemokines, cytokines, and cells included in this mechanism, including the healing process. Lung injury in burn patients, especially acute respiratory distress syndrome (ARDS) was the final process of the mechanism that end with alveoli damage, fluid accumulation, and bronchospasm. Clinicians need to do a quick diagnostic approach by the sign and symptoms to save the patients. However, studies suggested it was not efficient enough to had some radiological findings to determine the stage of acute respiratory distress syndrome. The principal therapy of acute respiratory distress syndrome related to burn injury is to secure the airway and to maintain breathing mechanism of the patients by ventilation therapy. The pharmacological approach targeting the inflammatory cytokines are not giving enough evidence to be considered the treatment of choice. Therefore, we encourage for future research to understanding more about acute respiratory distress syndrome in burn patients with focusing on significant inflammatory response in burn patients for marker to diagnostic and research about pharmacological approach in these patients.

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