Standards in Biologic Lesions: Cutaneous Thermal Injury and Inhalation Injury Working Group 2018 Meeting Proceedings

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On August 27 and 28, 2018, the American Burn Association, in conjunction with Underwriters Laboratories, convened a group of experts on burn and inhalation injury in Washington, DC. The goal of the meeting was to identify and discuss the existing knowledge, data, and modeling gaps related to understanding cutaneous thermal injury and inhalation injury due to exposure from a fire environment, and in addition, address two more areas proposed by the American Burn Association Research Committee that are critical to burn care but may have current translational research gaps (inflammatory response and hypermetabolic response). Representatives from the Underwriters Laboratories Firefighter Safety Research Institute and the Bureau of Alcohol, Tobacco, Firearms and Explosives Fire Research Laboratory presented the state of the science in their fields, highlighting areas that required further investigation and guidance from the burn community. Four areas were discussed by the full 24 participant group and in smaller groups: Basic and Translational Understanding of Inhalation Injury, Thermal Contact and Resulting Injury, Systemic Inflammatory Response and Resuscitation, and Hypermetabolic Response and Healing. A primary finding was the need for validating historic models to develop a set of reliable data on contact time and temperature and resulting injury. The working groups identified common areas of focus across each subtopic, including gaining an understanding of individual response to injury that would allow for precision medicine approaches. Predisposed phenotype in response to insult, the effects of age and sex, and the role of microbiome could all be studied by employing multi-omic (systems biology) approaches.

The Underwriters Laboratories (UL) Firefighter Safety Research Institute (FSRI), as well as the Bureau of Alcohol, Tobacco, Firearms and Explosives (ATFE) Fire Research Laboratory, have developed expertise, data, and best practices on fire dynamics and investigation, firefighting practices, and building construction. Despite this work, causal relationships between variable thermal or chemical exposure and extent of injury to the human body have not been well characterized. Seminal work in the 1940s and 1950s attempted to define the characteristics of injuries that would result from specific thermal exposure parameters,1–3 but over the years this work has been misapplied and misinterpreted.4–6 In half of a century, the work has not be readdressed, perhaps due to the more recent development of tools and methods for measurements with increased accuracy and precision, as well the availability of adequate translational models. Regardless, questions remain regarding what combinations of temperature, exposure mechanism, and duration will result in a given depth of cutaneous injury. Similarly, there are unknowns regarding what amount of which combustion products under what environmental conditions will result in an injury. Similarly, there are unknowns regarding what amount of which combustion products under what environmental conditions will result in an injury. Similarly, there are unknowns regarding what amount of which combustion products under what environmental conditions will result in an injury. Similarly, there are unknowns regarding what amount of which combustion products under what environmental conditions will result in an injury.

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conditions (space, temperature, and humidity) will result in inhalation injury and the extent of that injury. To elucidate these relationships, well-characterized model systems that can serve as a surrogate for human pathophysiology and allow for variables to be tested in both isolation and combination should be used.

In order to better define and address these gaps, which cover a broad range of expertise and involve many variables that must be analyzed, a consortium among prominent researchers and experts was formed. Through UL, the International Association of Fire Fighters, and the American Burn Association (ABA), the working group was convened. The goals of the meeting set forth by UL were to identify research endeavors that will yield a standard set of data on fire environment exposure and resulting injury characteristics that can be used in setting industry standards and aid in investigations. During the development of the workshop, the Research Committee of the ABA proposed the addition of two more areas where discussions on research needs and knowledge gaps by this already convened group would benefit the burn community and help define a research agenda. This resulted in four focus areas: Basic and Translational Understanding of Inhalation Injury, Thermal Contact and Resulting Injury, Systemic Inflammatory Response and Resuscitation, and Hypermetabolic Response and Healing.

Participants had expertise and experience that broadly covers translational animal modeling for cutaneous thermal injury and inhalation injury and other facets of burn research including resuscitation, critical care, hypermetabolism, and wound healing. Each participant brought forward their past experience and findings, and most importantly insight on the state of the science as well as optimal models and studies for answering the questions that exist. By leveraging the already existing infrastructure and network of experts within the ABA, efficiency as well as rapid translation of knowledge and findings to clinical relevance and public knowledge is natural and probable.

The group met at Georgetown University in Washington, DC, on August 27 and 28, 2018 and began the meeting with presentations from UL and ATFE to gain perspective on the applied nature of their research on fire environment and exposure. Current research priorities and findings were shared, as well as examples of investigations. Areas where there are needs for more data and guidance from the burn research community were highlighted and discussed, specifically related to predicting and understanding the injury phenotypes that result from various exposure conditions. Importantly, the need for appropriate application of this data to aid in forensic and medical legal investigations, as well as predictive models for injury prevention, was reviewed in order to give the burn care participants better context and understanding of how their research and data are applied in the field. Speakers from each of the four subject matter areas were then called on to provide an introduction to the state of the science in each of the topics. Subsequent work was performed in breakout groups where further discussion of the science, current barriers and challenges, and future research priorities were defined. These are reported here as a summary of the meeting proceedings and conclusions from each discussion area.

KNOWLEDGE GAPS IN FIRE SCIENCE AND ENGINEERING

Engineering and Burn Injuries: Where Are the Gaps

Presented by Daniel Madrzykowski, PhD, PE

The UL FSRI has been conducting research to develop knowledge leading to best practices for firefighting and improved understanding of the dynamics of structure fires. One factor in determining the best firefighting practice is the impact on a civilian or firefighter who may be trapped in the structure that is on fire. Investigations of fire incidents provide another means to better understand fire dynamics and the effectiveness of firefighting tactics. In many cases, studying the thermal injuries to civilians or firefighters could be critical to understand the environment to which victims were exposed.

From a fire protection engineering perspective, the data available to estimate conditions that can result in burn and inhalation injuries are more than 50 years old.1–3,7,12 Recent literature in the medical field that uses computational methods to assess burn injury still depends on the data from Henriques and Moritz,1–3,9–12 Stoll,8 and others.7 Measurement capabilities have changed during the past 50 years. Contact and noncontact thermal sensors, gas analysis instruments, and data acquisition systems have all improved since the foundational burn injury research was conducted during the 1940s through the 1960s.

In the past 50 years, the fire environment, where the injured individuals are found and where the firefighters work, has changed considerably. Changes in building construction materials and methods, focus on energy efficiency, and foam plastic furnishings have changed the nature and the speed of fire growth within a structure. Today, a fire in a residential structure is fueled predominantly by home furnishings made of synthetic materials, while historically natural fibers such as cotton were more common.

To compare the speed of fire growth and the magnitude of the heat release rate between a sofa padded with cotton fiber and a sofa padded with synthetic materials, UL FSRI burned them under an oxygen consumption calorimeter to measure the heat release rate. Figure 1 shows three pairs of images of the two sofas. The top set of images were captured at 1 minute after ignition with a small open flame. The flame in the sofa made of synthetic materials is slightly larger than the flame in the natural fiber sofa. The second pair of images were recorded at 3 minutes after ignition. At this point the horizontal flame spread on the cotton sofa was within 6 inches of the point of ignition on the sofa cushion, while one of the polyurethane seat cushions on the other sofa was well involved in fire and had melted and spread the fire to the floor. The final pair of images show the extent of the fires at 4 minutes and 30 seconds after ignition. The fire in the cotton sofa had not changed much in the preceding 90 seconds and the heat release rate was less than 100 kW. In contrast, the sofa with polyurethane seat cushions was fully involved in fire and had a peak heat release rate of approximately 4000 kW.

The impact of this type of rapid fire growth in the synthetic sofa scenario is that a house with adequate ventilation could undergo flashover within 3 to 5 minutes of ignition.
A flashover is a transition where the fire environment in a room changes from an untenable hot gas upper layer and cool tenable air layer near the floor to a well-mixed, burning gas layer extending from the ceiling down to the floor with temperatures in excess of 600°C and with heat fluxes ranging from 60 to 200 kW/m². This environment is considered untenable even for a fully protected firefighter. While the same progression to flashover could occur in a home with the natural fiber cotton sofa being the source of fire, we expect based on these data that it would likely take 20 minutes or more for the fire to create a similar level of hazard within the structure.

While the physics of fire itself remain unchanged, changes in home and furnishing construction have had a significant impact on fire dynamics and on the fire hazard exposure. With these changes, what is needed by the fire protection engineering community to better understand what combinations of thermal energy, exposure mechanism, and duration result in what depths of cutaneous injury. Similarly, the amount of thermal energy (heat, humidity, and time) resulting in an inhalation injury would aid in our assessments. Help is needed from the burn research community in answering a range of questions to address the following:

- The adequacy of current burn injury datasets.
- The accuracy of engineer interpretation of the data.
- The role of heat transfer method (conduction, convection, or radiation) in burn injury phenotype.
- The status of development and validation of burn prediction models.
- Is there a need for a skin model as well as a trachea model?

Figure 1. Set of images showing the growth rate of fires in a sofa with cotton padding (left) and in a sofa with polyurethane foam and polyester padding (right). Three times are shown after ignition of the fire starting from the top: 1, 3, and 4.5 minutes.
thermal contact variables and the resulting cutaneous injury, the data and literature available on chemical exposures (environmental levels) and resulting physiologic levels and non-cutaneous pathophysiologic impacts are similarly outdated or nonexistent. Carbon dioxide, carbon monoxide, and oxygen levels are all routinely measured in fire simulations, but hydrogen cyanide is harder to measure and therefore less frequently analyzed, though acknowledged as a potential biomarker of exposure as well as a potential therapeutic target (i.e., Cyanokit). Lack of ability to readily assess such potentially important analytes presents an additional challenge in retrospectively determining the circumstances that resulted in the phenotype of injuries found in victims coming out of a fire environment. Rodent model data, including LC50, are often the most complete data available that engineers have to work with when translating environmental exposure data to potential or predicted injuries. An additional question of relevance to fire investigations is regarding accelerant use compared to non-accelerant fires and the differences in terms of inhaled toxic chemicals. To date, there are no widely used standardized datasets that can be referenced for these purposes in fire scene investigation.

Empirical predictions of burn injury are used for estimating timing of ignition, exposure duration, and other fire-related parameters that meet a threshold that is calculated to result in a “full thickness burn.” In order to validate the accuracy of these assessments, an important question for each scenario in which the empirical formulae are used would be, is this equation testable in an animal or other controllable model?

**TOPIC 1: BASIC AND TRANSLATIONAL UNDERSTANDING OF INHALATION INJURY: AIRWAY THERMAL INJURY, SMOKE INHALATION, TOXINS, AND LATE EFFECTS**

Moderators: Jeffrey Shupp, MD, Mashkoor Choudhry, PhD

Despite advances in the care and resuscitation of thermal cutaneous injury, strategies to treat inhalation injury have not similarly evolved and are inconsistently applied. Much of this uncertainty is due to the lack of uniform and objective criteria for the diagnosis of inhalation injury, as well as an incomplete understanding of the underlying pathophysiology and long-term effects.

The group identified three areas of incomplete understanding of the underlying pathophysiology and long-term effects: 14-17

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  - **Airway repair mechanisms:** the airway microbiome, and biomarkers of inhalation injury.

  - **Thermal/cutaneous injury:** strategies to treat inhalation injury have not similarly evolved and are inconsistently applied.

  - **Failure to rapidly assess potentially important analytes:** presents an additional challenge in retrospectively determining the circumstances that resulted in the phenotype of injuries found in victims coming out of a fire environment.

  - **Rodent model data:** including LC50, are often the most complete data available that engineers have to work with when translating environmental exposure data to potential or predicted injuries.

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Rat models have revealed that by 1 day after smoke inhalation injury, BALF microRNAs involved in acute respiratory distress syndrome, pulmonary fibrosis, endothelial cell regulation, and apoptosis as well as pulmonary tissue circular RNAs modulating these microRNAs are differentially regulated.\(^{43,44}\)

In conclusion, a framework is needed to guide future investigations of the diagnosis and pathophysiology of inhalation injury. Identification of the specific factors guiding stem cell regeneration of injured tissues may allow bioengineering of pulmonary tissues. Understanding how the airway microbiome maintains healthy respiratory mucosa and its response to injury may generate treatments to restore normal flora following dysbiosis. Finally, analysis of the patterns of release of cytokines and other protein or RNA markers and how these patterns differ between the pulmonary and systemic responses may allow differentiation of inhalation injury severity or even predict the development of complications or mortality. However, a single specific or even set of biomarkers that can be used to definitively diagnose inhalation injury remains elusive.

**TOPIC 2: WHAT DOES IT TAKE TO CAUSE CUTANEOUS PATHOLOGY: CONTACT TIME, SOURCE, AND EXPECTED SKIN DAMAGE**

**Moderators: Angela Gibson, MD, PhD, Heather Powell, PhD**

Predicting the extent of injury based on temperature and time of contact is critical to forensic and medical legal investigations but also for the development of personal protection equipment to properly protect firefighters. Literature on models and data supporting the time and temperature needed to generate a specific depth of burn injury were reviewed. Historically, the Arrhenius model predicts that cellular death occurs at 43°C, but it is unclear if this translates into what happens to cells and structures located within a living tissue. Additional mathematical/computational models have been developed to predict the extent of injury based on contact time and temperature, however these models rely on assumptions and input data that can result in the propagation of errors if the input data are incorrect.

The group further reviewed the seminal work of Moritz and Henrique, which has been cited in countless papers on thermal injury and contact time. On close inspection of this work, it is apparent that the descriptors used to designate different depths of cutaneous injury are problematic. Specifically, the terms second- and third-degree reactions were used in these original manuscripts to describe epidermal and transepidermal necrosis and are not equal to second- and third-degree burns extending into or through the dermis. Unfortunately, as detailed by Abraham, these misnomers have persisted to this day in the scientific literature and are widely adopted for litigation and safety legislation related to thermal injury.\(^4\) In the mid to late 20th century, the military was heavily involved in testing and modeling thermal injury and contact time. For example, Stoll and Chianta, at the Naval Air Development Center, used modeling to identify that Moritz and Henrique failed to account for the damage that occurred to skin after the thermal source was removed, which accounts for one third of the total damage at high heat per their estimation.\(^6\) Thus, the models based on Moritz and Henrique may significantly underestimate the true depth of injury and more extensive validation of these models must be conducted.

To overcome challenges associated with human studies, animal models are used extensively in burn research. Despite the vast differences in anatomy of the skin, the use of rodent models to study wound healing in thermal injury is common. Porcine skin is much closer anatomically and functionally to human skin; however, a systematic review on comparing various burn porcine models revealed a major concern regarding the reproducibility of burn depth and severity.\(^45\)

Overall, limitations in the body of literature associated with contact time and depth of burn injury are numerous. The animal studies are small, and the variations in methodology (temperature, time, pressure, source of heat) and animal used (breed, age, location of injury) make comparisons across studies difficult. Mathematical modeling is less expensive than animal models; however, there is an increased risk of error with complex situations that require many assumptions. Gaps in knowledge include direct comparisons of human and porcine burn injury, the study of burn evolution over time, and what depth of injury means to regeneration and wound healing.

Three initiatives were proposed to develop a set of reliable data of thermal injury as it relates to contact time and temperature, with the overall goal to reproduce initial data for use as baseline for injury patterns in safety and litigation literature, as well as enhance the rigor and reproducibility to the burn research community.

1. Clarify the role of pig breed in response to thermal injury with the goal of identifying the breed with greatest homology to human skin.
2. Using the identified in vivo model from above, compare thermal injury method—contact, scald, and radiant exposures at a specific temperature and time.
3. Characterize the relationship between time and temperature, and the resultant injury using the in vivo model to develop standards for future investigations and research.

In summary, the group identified a critical need to repeat and improve on historical experiments for standardization purposes. In addition to the above, a standard method of determining cellular damage is also necessary, as the current method of interpretation of cellular injury with hematoxylin and eosin staining is challenging. Several questions arose during the discussion including how the anatomic location for burn injuries will be determined, and an acknowledgement that age and sex factors must be considered. Finally, a need for a standard device/implement that delivers consistent results across different laboratories was identified.

**TOPIC 3: THE INFLAMMATORY RESPONSE TO CUTANEOUS BURN AND INHALATION INJURY: WHAT MODELS ARE NEEDED TO MOVE THE NEEDLE ON RESUSCITATION AND MODULATION OF HOST RESPONSE**

**Moderators: L. Cancio, MD, Charles Wade, PhD**

Based on reviewing the literature and discussions of the previous and current research, this group identified three areas of emerging laboratory and clinical research which are understudied...
and which could impact care and outcomes. The first is catecholamine control. Thermal injury is well-known to elicit massive and sustained release of catecholamines. The production of catecholamines correlates with the degree of hypermetabolism (increased energy expenditure) and hypercatabolism (lean body mass loss) following injury. Efforts to meet the caloric requirements generated by an increased metabolic rate and the nitrogen requirements generated by increased lean body mass turnover are not fully able to prevent the adverse effects. Thus, beta-blockade with propranolol has emerged as a way to blunt the effects of catecholamines. The effects of catecholamines at the cellular level, and the ideal way to manage these effects, are not fully understood. For example, both vagal nerve stimulation and an agonist of the $\alpha_7$ acetylcholine receptor attenuate muscle wasting following thermal injury in murine models. The clinical impact of these findings is unknown.

Second, neuroinflammation is an understudied problem with potential for significant impact on postburn quality of life. The systemic inflammatory response syndrome that typifies the body’s response to thermal injury affects all organs in the body, not the least of which is the central nervous system. Even in the absence of traumatic brain injury, patients with extensive burns may sustain disruption of the blood–brain barrier, which may lead to increased intracranial pressure during the resuscitation period. Increased expression of pro-inflammatory mediators such as tumor necrosis factor-$\alpha$, IL-1$\beta$, and intercellular adhesion molecule-1, as well as the matrix metalloproteinases MMP-2 and MMP-9, was associated with blood–brain barrier breakdown and cerebral edema. These effects may contribute to the high rate of delirium in burn patients over the short term, as well as to the high rates of neurocognitive disorder and posttraumatic stress disorder in survivors. Clinical interventions directed at controlling neuroinflammation do not exist. Applicability to this area of decades of traumatic brain injury research should be explored.

Third, illness prediction (who gets sick and why) is an important unresolved problem in the care of thermally injured patients. Comorbidities complicate the care of many burn patients. These may include frailty due to advanced age and inactivity, diabetes mellitus, hypertension, obesity, substance abuse, and polytrauma. Yet, much prospective burn research is designed to exclude such patients from study. To this should be added the effects of sex on outcome, which are not fully understood. Outcome prediction is hampered by nosological problems, such as disagreements about how best to define infection. Finally, our understanding of the role played by genetics in survival after thermal injury is in its infancy.

In summary, optimal patient care will require a better understanding of the interaction between genetics, preexisting conditions, and outcome.

**TOPIC 4: WHAT WE HAVE LEARNED ABOUT THE HYPERMETABOLIC RESPONSE FOLLOWING BURN INJURY: IMPLICATIONS ON WOUND HEALING AND SCAR**

**Moderators:** Celeste Finnerty, PhD, Matthias Majetschak, MD, PhD

Hypermetabolism in burn patients is well documented, having been studied in clinical trials and translational models from the perspectives of both the mechanisms that cause the response as a result of burn injury, and also the downstream effects. Despite this, several unknowns remain when it comes to the interplay of a hypermetabolic response and both acute and chronic impacts of systemic pathophysiology including muscle wasting and cardiac dysfunction, as well as outcomes of hypertrophic scarring and rate of wound closure. Unlike other traumatic insults that induce metabolic dysfunction that resolves within days to weeks after exposure, it has been shown that burn-induced metabolic dysfunction persists for months to years after injury even at the molecular level. This impacts not only the acute care of the burn patient but also longer term rehabilitation. Pharmacologic, surgical, and nutritional interventions have been proposed to mitigate postburn hypermetabolism and the associated effects.

In agreement with the discussion by the group on Topic 3, several points regarding postburn catecholamine control, neuroinflammation, and physiologic differences related to age and sex were re-emphasized as they relate to hypermetabolic response. Building on the issue of catecholamine release as a result of burn injury, it is important to note the breadth of downstream impacts including those mediated through the beta-adrenergic receptor. An example is cardiac dysfunction postburn, postulated in the literature to be the result of this cascade, with a significant body of evidence described in rodent models. An elevated innate immune response, apoptotic activity, and systemic inflammation also play roles in downstream pathophysiology, perhaps contributing synergistically to cardiac dysfunction, cachexia, hyperglycemia, and hyperinsulinemia.

Links between a prolonged hypermetabolic response and hypertrophic scarring were discussed. Evidence exists that demonstrates abrogating the hypermetabolic response using oxandrolone and propranolol in combination can diminish scar pathology in patients, among other previously reported positive impacts of this drug regimen in mitigating hypermetabolic effects. The proposed mechanisms are linked to a more rapid rate of wound closure as well as a mitigation of the energy resources required in a lengthy scar remodeling process.

In order to increase the knowledge on mechanisms of hypermetabolic response in burn patients, with a goal of identifying effective therapeutics, the group identified the following research priorities:

1. Elucidate how the burn-induced perturbations of drivers of the hypermetabolic response and neurohormonal signaling affect organ systems.
2. Characterize sex and age differences in the response to burns by establishing adequate models (extremes of age included—neonatal, middle age, elderly).
3. Develop personalized burn care approaches including pain control (with consideration of pain sensitivity, opioid tolerance) and modulation of the hypermetabolic response.

Critical to addressing each of these priorities are translational models that allow for the study of both acute and long-term impacts of metabolic dysfunction. The models that are used must be well suited to also allow for the measurement of relevant outcomes, with injuries that are severe enough to induce translatable long- and short-term pathophysiology.
SUMMARY

A broad range of topics were covered at this meeting of translational research experts in each area. The meeting was convened with a goal of identifying research priorities that not only will lead to improved burn care, but also contribute to the presently inadequate body of literature that is available to colleagues in fire protection engineering and fire scene investigation on expected pathologic impacts of thermal exposure and injury. The topic areas and gaps were identified by the Research Committee of the ABA, in collaboration with the UL. It is acknowledged by the authors and participants that the research areas identified in the present manuscript are not fully comprehensive, as Burn Research needs are also currently being systematically analyzed by Delphi Panels; however, the present work is expected to contribute to the overall shaping of a burn research agenda or trajectory, specifically for the members of the ABA.

Overarching findings of the group included a need for biomarkers that can be used to definitively diagnose inhalation injury, consideration of the microbiome role in injury and healing, the need to establish standard datasets on cutaneous injury phenotype resulting from specific contact variables, consideration in modeling for age and sex differences in response to injury, and acknowledgement that patients have comorbidities that may not be reproducible to their full extent in animal models. The work that started at this meeting, described here in the proceedings, will be continued by the participants and supported by the ABA through further collaborative efforts.

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