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REVIEW ARTICLE

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Systemic immune response of burns from the acute to chronic phase

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Abstract

Immune responses that occur following burn injury comprise a series of reactions that are activated in response to damaged autologous tissues, followed by removal of damaged tissues and foreign pathogens such as invading bacteria, and tissue repair. These immune responses are considered to be programmed in living organisms. Developments of modern medicine have led to the saving of burned patients who could not be cured previously; however, the programmed response is no longer able to keep up, and various problems have arisen. This paper describes the mechanism of immune response specific to burn injury and the emerging concept of persistent inflammation, immunosuppression, and catabolism syndrome.

KEYWORDS

compensatory anti-inflammatory response syndrome, DAMPs, PAMPs, persistent inflammation, immunosuppression, and catabolism syndrome, systemic inflammatory response syndrome

INTRODUCTION

Burns are responsible for 180,000 deaths annually worldwide and are considered a global public health problem by the World Health Organization.[1] Guidelines for burn care include those of the Japanese Society for Burn Injuries, American Burn Association, European Burns Association, and International Society for Burn Injuries.[2–5] However, the complexity of the pathogenesis remains an important clinical challenge. Severe burns cause severe inflammation in the acute phase, followed by a complex biological response, with inflammation and hypermetabolism lasting for several months or longer.[6] Burn patients are referred to as the "universal trauma model," causing extensive soft tissue damage with shock, and the magnitude of physiologic changes induced by the injury reliably reflects what percentage of the total body surface area (TBSA) has been burned.[7]

The primary role of the immune system is to protect the body from infection and various diseases, followed by activation of repair mechanisms with the ultimate goal of restoring tissue homeostasis.[8,9] In extensive burns, the immune system is activated not by pathogens but by the injured tissue itself. Specific immune responses are triggered to protect the body from excessive inflammatory reactions and persistent tissue disintegration.[10,11] Severe burns are known to induce early and persistent inflammatory reactions in more than 90% of patients,[12,13] with the predominant inflammatory response being termed systemic inflammatory response syndrome (SIRS), and the predominant anti-inflammatory response being termed compensatory anti-inflammatory response syndrome (CARS). Excessive levels of these responses can lead to complications such as shock, multiple organ failure, and mortality.[13,14] As advances in medical care have allowed patients with severe burns to survive the acute phase, chronic mortality has become a problem. Thus, the theory of SIRS-CARS-PIICS (persistent inflammation, immunosuppression, and catabolism syndrome) has been proposed (Figure 1).[15]

BURNS AND IMMUNE RESPONSE

The discovery of innate immune receptors[16] and recognition of molecular patterns of self-tissue as danger signals[17] have made it possible to immunologically understand such

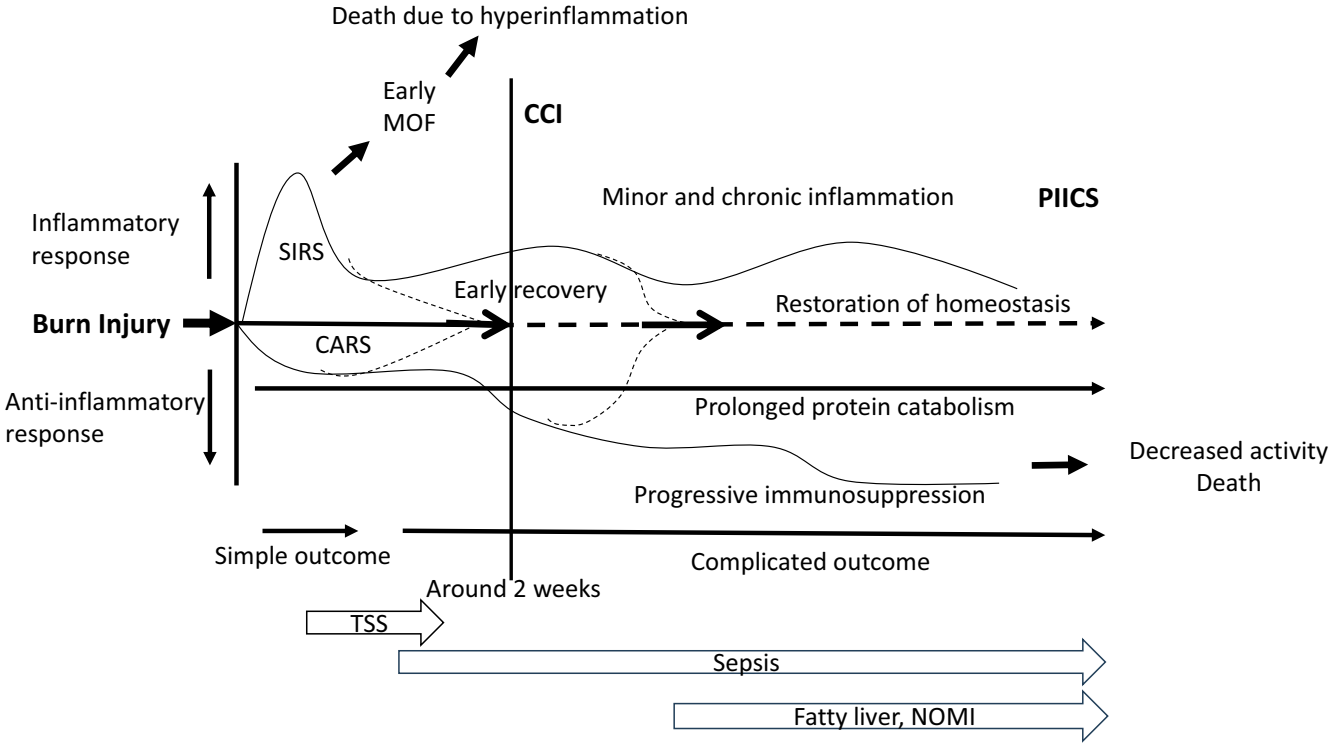

FIGURE 1 Diagram of the immune response following burn injury. A two-hit response during the SIRS phase leads to inflammatory multiorgan failure. Relatively small burns have a simple outcome of wound closure and healing without complications, but usually have a complex outcome with many complications. After the initial SIRS inflammatory and CARS anti-inflammatory responses, many patients present with a clinical picture of protein loss, malnutrition, delayed wound healing, and recurrent infections. In addition, there is a persistent inflammatory response and dysfunction of both innate and acquired immunity. Clinically, early complications include TSS, followed by sepsis, fatty liver, and NOMI after about 1 month. Convergence to a state in which both inflammatory and anti-inflammatory responses are abolished leads to a cure. CARS, compensatory anti-inflammatory response syndrome; CCI, chronic critical illness; NOMI, non-obstructive mesenteric ischemia; PIICS, persistent inflammation, immunosuppression, and catabolism syndrome; SIRS, systemic inflammatory response syndrome; TSS, toxic shock syndrome.

non-infectious inflammation as burns. After toll-like receptors (TLRs) were identified, various pattern recognition receptors (PRRs) were discovered, and the immune system recognizes not only foreign microorganisms but also molecules released from autologous tissues as danger signals.[17] The concept of immune responses driven not only by exogenous substances such as bacteria but also by endogenous danger signals has greatly changed the recent understanding of immunology.[18] Pathogen-associated molecular patterns (PAMPs) are substances not existing in humans but that trigger immune responses in them, whereas damage-associated molecular patterns (DAMPs) induce "sterile inflammation".[19] While PAMPs are exogenous substances, DAMPs are basically endogenous self-substances. In burn patients, tissue damage due to thermal and mechanical injury, ischemia, and reperfusion injury releases various DAMPs.[20] Those derived from damaged tissue that are released extracellularly recognize molecular patterns of foreign microorganisms such as TLRs, The nucleotide-binding oligomerization domain-like receptors (NOD-like receptors: NLRs), and the retinoic acid-inducible gene I (RIG-I-like receptors) of antigen-presenting cells, which are the executing cells of the innate immune system recognized by PRRs.[21–23] Through the action of various cytokines, activated antigen-presenting cells diversely alter the phenotype of T cells of the adaptive immune system, resulting in progression of both an inflammatory response and an anti-inflammatory response.[10,11,24] After SIRS is induced by the innate immune system, CARS occurs as a feedback mechanism to maintain immune system homeostasis,[25] but in reality, SIRS and CARS mix in a state called mixed antagonistic response syndrome, and these processes are now thought to occur almost in parallel.[20,25,26] The patient's immune status then moves toward stabilization but does not return to homeostasis; rather, it progresses to PIICS, which increases the risk of organ failure and sepsis when persistent inflammation, immunosuppression, and hypercatabolism are sustained (Figure 2).[15]

BURNS AND INNATE IMMUNITY

Severe burns, trauma, and mechanical tissue injuries such as major surgery induce similar intense inflammatory/immune responses.[11,25,27] Innate immunity causes the initial immune response in the acute phase, which is initiated by antigen-presenting cells, mainly macrophages and neutrophils, recognizing DAMPs released from the injured tissue via PRRs.[23,26,28,29] Many of these autologous tissue-derived DAMPs (Table 1) activate immunocompetent cells by signaling through PRRs such as TLRs, NLRs, receptors

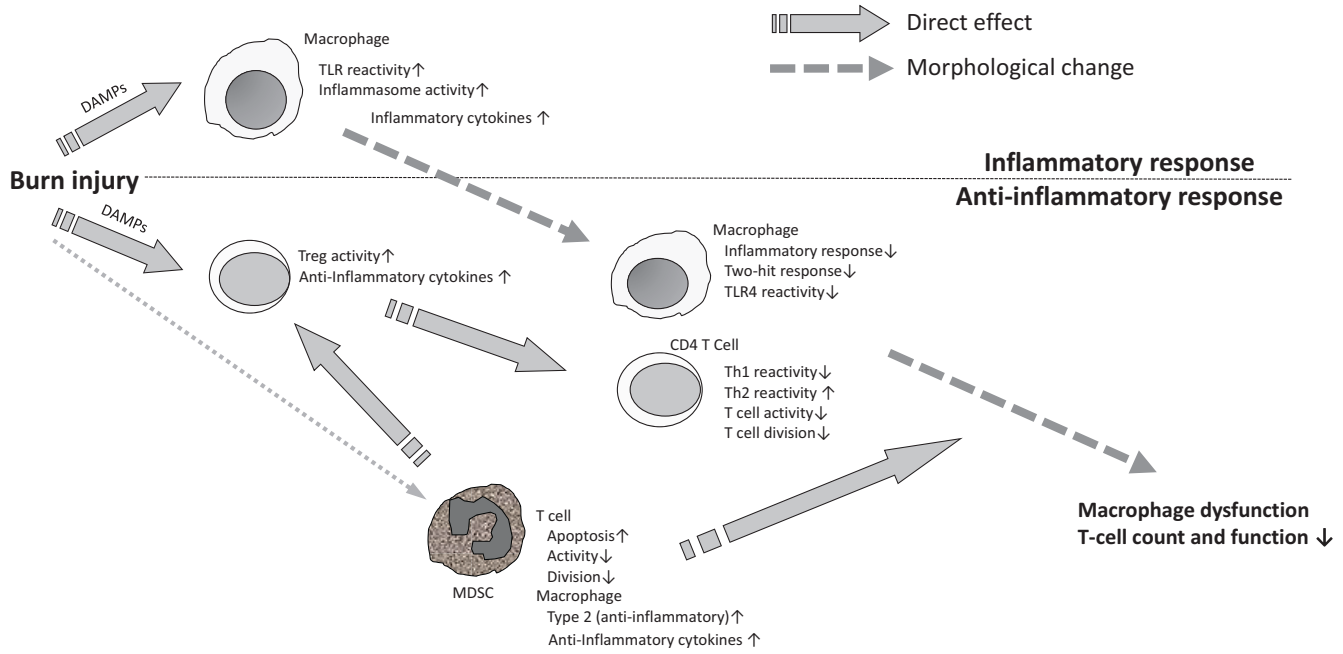

FIGURE 2 Immune cell changes following burn injury. DAMPs released from tissue damage such as burn injuries induce inflammation mainly by activating macrophages of the innate immune system. DAMPs activate immunocompetent cells by signaling through PRRs such as TLRs and inflammasomes, which increase the release of multiple inflammatory mediators (IL-1, IL-6, IL-8, IL-18, TNF-γ, etc.). At the same time, Lymphocytes responsible for cellular immunity are decreased, but Th2 is increased due to increases in IL-4 and IL-10 and decreases in IL-2 and IFN-γ. And Tregs of the acquired immune system are also activated to control excessive inflammation. However, when bone marrow-derived stem cells are rapidly differentiated, they release MDSCs. MDSCs enhance Treg function and suppress macrophage and T-cell function, leading patients to a state of PIICS. DAMPs, damage-associated molecular patterns; IFN, interferon; IL-, interleukin-; MDSCs, myeloid-derived suppressor cells; PIICS, persistent inflammation, immunosuppression, and catabolism syndrome; PRRs, pattern recognition receptors; TLRs, toll-like receptors; TNF-α, tumor necrosis factor alpha; Tregs, regulatory T cells.

TABLE 1 DAMPs and PRRs associated with burns/trauma.

Origin	DAMPs	PPRs
Cytosol	Uric Acid	NLRP3, P2X7
	HSPs	TLR2,4, CD91
Mitochondria	Mitochondrial DNA	TLR3,7,8,9, RAGE
	ATP	P2X7, P2Y2
Nucleus	HMGB1	TLR2,4, 9, RAGE
	Histone	TLR2,4, 9, NLRP3
ECM	Hyaluronan	TLR2,4, RAGE

Abbreviations: ATP, adenosine triphosphate; DAMPs, damage-associated molecular pattern molecules; ECM, extracellular matrix; HMGB1, high mobility group box 1; HSPs, heat shock proteins; NLRP3, Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing 3; PRRs, pattern recognition receptors; RAGE, receptors for advanced glycation end products; TLR, toll-like receptor.

for advanced glycation end-products, and purinergic receptors.[22,30–34] When DAMPs are recognized by PRRs, downstream inflammatory pathways are activated via adaptor proteins such as MyD88 (myeloid differentiation factor 88) and TRIF (TIR domain-containing adaptor inducing interferon-β), which are involved in the release of multiple inflammatory mediators (IL-1, IL-6, IL-8, IL-18, TNF-γ, etc.), and master transcription factor NF-κB, and the activation of interferon (IFN) regulatory factor is triggered.[28,35]

High mobility group box 1 (HMGB1), the most widely studied nuclear protein, is recognized by multiple PRRs, mainly TLR4, and it is reported that acute lung injury is reduced in TLR4 knockout models with a decrease in burn-induced lung neutrophil infiltration.[36] Mitochondrial DNA released from damaged tissue has been shown to activate neutrophils via TLR9 to induce inflammation.[32] Mitochondrial DNA is also reported to produce the inflammatory cytokines IL-1β and IL-18 by activating the NLRP3 inflammasome via NLRs.[37] Many other DAMPs are also released by burn injury and are correlated with cytokines such as IL-6, IL-10, and TNF-α.[22,23] Inflammasomes, one type of PRRs, induce the release of inflammatory cytokines and also programmed cell death called pyrolysis.[38] Inflammasome activation begins immediately after injury, increases with burn severity,[6,39,40] and its activity appears to be necessary to protect the body from burns.[40]

Immunosuppression in critically ill patients involves activation of myeloid-derived suppressor cells (MDSCs), mesenchymal stem cells (MSCs),[41,42] depletion of inflammatory cells by apotosis,[43] and anti-inflammatory cytokines. MSCs have immunomodulatory properties, and MSCs administered in wound models are reported to reduce inflammatory cytokines such as IFN-γ, TNF-α, and IL-6, suppress inflammatory responses, and promote wound healing.[44] Macrophages differentiate into M1 and M2 macrophages depending on the environment. M1 is a conventional

macrophage differentiated by TNF-α and IFN-γ, whereas M2 is differentiated by IL-4 and IL-13. M2 acts in an inhibitory manner by secreting anti-inflammatory cytokines such as IL-10, TGF-β, and IL-1Ra and is also importantly involved in changes in the adaptive immune system and tissue repair.[45] However, while these immunosuppressive mechanisms suppress excessive inflammation, excessive immunosuppression is reported to result in a poor prognosis in cases of decreased expression of MHC-II (HLA-DR) in macrophages.[8,46]

BURNS AND ADAPTIVE IMMUNITY

Suppressive changes centered on T cells regulate the immune environment after burn injury, and immunosuppressive functions of helper T cells (Th), such as the change of immune response from Th1 to Th2, anergy and exhaustion of T cells, and activation of regulatory T cells (Tregs), are reported.[25,47,48] Prolonged immunosuppression due to prolonged loss of function of these T cells is one of the pathogeneses of PIICS. In the acute phase of severe burn, neutrophils are increased and lymphocytes responsible for cellular immunity are decreased, but not all lymphocytes are decreased; Th2 is increased due to the increases in IL-4 and IL-10 and decreases in IL-2 and IFN-γ. The increase in Th2 after burn injury suppresses the activity of inflammatory Th1, which underlies the cellular immune response.[49] Both Th17 and Tregs are induced to differentiate by TGF-β during the differentiation process, but high levels of IL-6 inhibit differentiation into Tregs and promote differentiation of Th17.[50] These changes are closely related to the innate immune system because they depend on the cytokine environment. Although Th17 responses can be induced in burn-injured mice,[50] Tregs are reported to be increased and activated by burn injury.[41] Suppressive mechanisms induced by suppressive cytokines such as IL-10 and TGF-β and co-suppressive factors such as CTLA-4 and PD-1 are also reported.[10] Tregs are also reported to exhibit a unique phenotype of recognizing self-antigens during development and of expressing surface antigens such as already activated T cells. They are activated early in the invasion similar to innate immune cells, and their activation may be triggered through the T-cell receptors by self-antigens.[51,52]

GENETIC ANALYSIS OF BURN PATIENTS

From gene expression studies, burn patient samples were grouped and analyzed at 0–1, 1–2, 2–4, and 4–7 days, indicating that inflammation/immune-related processes were enriched for at least 1 week after injury. In contrast, cell activation-regulated processes were enriched at later time points.[53] In a mouse model of burn injury, inflammatory response genes such as IL-6, IL-8, and IL-1β were also expressed. In addition, processes that enhance metabolism and catabolism were expressed.[54] In a study comparing microarray data from the Glue Grant Trauma-Related Database to 10 elderly patients ($n = 10$) and a sex- and TBSA burned -matched adult control group ($n = 20$), differential expression between the elderly and adult groups. A number of immune-related pathways were downregulated, including those associated with antigen processing via MHC class I, ubiquitination, and proteasomal degradation. Cellular signaling pathways, including NF-κB, C-type lectin receptor, and T-cell receptor signaling, were also significantly decreased in elderly burn patients, as were pathways associated with antiviral immunity. Since many of the genes whose expression was increased in elderly patients with severe burns were associated with cellular pathways associated with destruction, such as complement activation and immunoglobulin production, the altered inflammatory and immune responses in elderly patients after burn injury indicate that elderly burn patients are unable to initiate an appropriate inflammatory and stress response in the acute phase after burn injury.[55] The gene expression analysis of 213 burn patients and 79 healthy controls revealed that down-regulated genes were enriched in the T-cell activation pathway, while up-regulated genes were enriched in the neutrophil activation response. Key genes that may be regulated by miRNAs (NFATC2, RORA, and CAMK4) were downregulated in burn patients. Expression of key genes was associated with the percentage of Th cells (CD4+) and survival and was a good predictor of burn prognosis.[56] In addition, proteomic analysis showed that hemoglobin Subunit α 1(HBA1), Transthyretin (TTR), and Serpin Family F Member 2 (SERPINF2) correlated with mortality outcomes, and are promising markers for the future.[57] These genetic and protein expression information are mainly studies that capture changes in the acute phase and support the immune response that has been discussed above. On the other hand, there are currently no studies on the association with mortality in the late phase, and future studies are expected.

PERSISTENT INFLAMMATION, IMMUNOSUPPRESSION, AND CATABOLISM SYNDROME

SIRS and CARS in the acute phase of invasion are biological reactions necessary to maintain function and tissue repair after burns. Usually, as the disease stabilizes, it gradually subsides and immune homeostasis is restored, but if it does not subside and immune homeostasis is not achieved after 2 weeks or more, it becomes a chronic critical illness (CCI), which is defined as PIICS (Table 2).[15] The pathogenesis of long-term chronic inflammation, immunosuppression, and catabolism in CCI includes persistent inflammation with persistent increase in MDSCs, immunosuppression due to decreased monocyte/macrophage and T-cell function, and protein catabolism with muscle wasting and cachexia similar to cancer and other chronic inflammatory diseases.[58] MDSCs are a heterogeneous population of

TABLE 2 Persistent inflammation, immunosuppression, and catabolism syndrome.[14]

Factor	Findings
Persistence	Prolonged hospitalization >14 days
Inflammation	C-reactive protein >150 μg/dL
Immunosuppression	Total lymphocyte count <800/mm^3
Catabolism	Weight loss of >10% during hospitalization or BMI <18 kg/m^2 Creatinine height index <80% Albumin <3.0 g/dL Pre-albumin <10 mg/dL Retinol binding protein <10 μg/dL

Abbreviation: BMI, body mass index.

immature myeloid cells that accumulate during conditions such as cancer and sepsis and are increased during emergency myelopoiesis.[59] It is thought that incomplete bone marrow cells containing MDSCs are produced during this phase of emergency myelopoiesis.[8,60] MDSCs produce the anti-inflammatory cytokines IL-10 and TGF-β, differentiate macrophages into anti-inflammatory type 2 cells, and promote Treg proliferation. In addition, they exert a strong immunosuppressive effect, such as by promoting the apoptosis of T cells.[61] The hypermetabolic state after burn injury is also reported to persist for up to 36 months after injury,[62] and stress hormones such as catecholamines can lead to persistent insulin resistance and increased glycogen, protein, and lipid breakdown. This results in increased resting energy expenditure, muscle wasting, protein loss, and increased acute-phase protein synthesis, ultimately leading to organ catabolism associated with organ dysfunction and death.[63] Even 6 months after injury, patients continue to show increased PD-1 expression on CD4+ T cells and decreased secretion of IL-6 and TNF-α with altered TLR expression on monocytes, indicating a persistent state of immunosuppression.[64] As there is no effective treatment for CCI,[65] it has become a social problem requiring long-term inpatient treatment without home care due to the severe disability caused. Studies show that the immune response in the acute phase after sepsis is equally abnormal in older and younger patients, but restoration of immune homeostasis is more difficult in older adults.[66,67]

KINETICS OF BLOOD CELLS FOLLOWING BURN INJURY

The observed data of blood cell counts in burn patients seem to indicate that the absence of platelet and lymphocyte counts after the injury is closely related to the outcome of mortality.[68] Platelets play important roles in several diverse processes other than hemostasis and thrombus formation, including promoting the interaction of inflammation and immune responses to both innate and acquired immune responses.[69,70] Anucleate platelets function as hemostatic cells in mammals, but in non-mammalian organisms, nucleated thrombocytes are involved in phagocytosis and in wound closure by forming blood clots and are thought to play a role not only in hemostasis but also as the first attacker of immunothrombosis, which removes foreign substances.[71] In severe burns, platelets may accumulate and cause complications because of vascular endothelial damage in multiple organs.[72–74]

BURNS AND VASCULAR ENDOTHELIAL DAMAGE

In severe burns, a systemic inflammatory response is elicited that causes vascular endothelial damage.[72–74] Endothelial cells form a barrier that controls permeability and plays a central role in the distribution of water, cells, and molecules from the circulation to the tissues, and they have a central role at the forefront of defense against danger signals in the innate immune response.[75] DAMPs activate PRRs expressed on endothelial cell surfaces,[76] immune cells, tissue macrophages, and monocytes to induce the initiation of inflammatory and coagulation cascades.[77]

ACUTE AND LATE COMPLICATIONS OF BURNS

Toxic shock syndrome (TSS)

Burns are at high risk for TSS because *Staphylococcus aureus* is a commensal organism of the skin. The post-injury onset of TSS occurs 2–4 days after the burn injury.[78,79] The incidence of TSS in children with burns is reported to range from 2.5% to 14%, and mortality can increase to 50% if TSS is not recognized and treated.[80] Total mortality rates for TSS in adults range from 30% to 80%, whereas lower mortality rates of 3%–10% are seen in children.[81,82] TSS is an immune response triggered by super antigens produced by *S. aureus* and *S. pyogenes*.[83] Super antigens can non-specifically activate T cells via the T-cell receptors, thus causing them to release large amounts of cytokines. Positivity for antibodies to toxic shock syndrome toxin 1 (TSST-1) is over 90% in adults but much lower in children, who are usually thought to have acquired antibodies by adolescence.[81] A study examining the development of TSS due to nosocomial MRSA infection in burn patients reported significantly lower TSST-1 antibody levels on admission and on the date of MRSA infection determination than in patients who did not develop TSS.[84] Clinicians should be alert to TSS because it occurs in all age groups, not just children, regardless of burn size.[85]

Sepsis

Sepsis is a fatal complication of burns and the leading cause of death after the first 24 h of injury. The prevalence of sepsis

in burn patients ranges from 26% to 65%.[21,86,87] The first line of defense of the innate immune system against pathogens is the anatomical barrier of the skin and mucosal epithelium before antigen-presenting cells and complement, but burns are reported to cause not only loss of the skin barrier but also damage to the intestinal epithelium.[88,89] In addition to disruption of the anatomic barrier, the combination of excessive inflammation and immunosuppression caused by DAMPs increases the mortality rate of sepsis in patients with severe burns.[89] The Surviving Sepsis After Burn Campaign guidelines, which were published in 2023,[90] provide 60 statements for guidance on 14 topics related to the early treatment of sepsis in burn patients.

Liver, pancreas, and gastrointestinal complications

Hepatic dysfunction and decreased albumin synthesis persist over the years and are thought to be caused by the fatty liver seen after burn injury. Burn injury causes hepatic injury due to hypoperfusion, inflammatory cytokines, edema, and fatty changes in the liver.[91] Fatty liver and hepatomegaly are seen in severely burned patients.[92–94] Fatty infiltration was found in 82% of patients undergoing liver biopsies and in 18% of patients with hepatic necrosis.[94] Gastrointestinal complications occur frequently in burn patients, and although the causal relationship is not clear in the previous reports, 25% of severe burns are considered affected by ulceration, bleeding, perforation, and mesenteric infarction.[95,96] Muschitz et al. reported that among 814 patients with severe burn, 17 patients developed intestinal infarction, 82% of which were due to non-obstructive mesenteric ischemia (NOMI). The mortality rate was 71%.[97]

Bacterial translocation

Following burn injury, organ blood flow is redistributed to vital organs and intestinal blood flow is reduced, exposing the intestines to a hypoxic environment and causing disruption of the intestinal epithelial barrier.[98] In severe burns, hypoperfusion and impaired motility of the intestinal tract were shown to cause certain Gram-negative aerobic bacteria to proliferate abnormally in the gut microbiota, thus altering the microbiota and compromising intestinal immunity.[99] These intestinal bacteria and endotoxins cause bacterial translocation by crossing the disrupted intestinal epithelial barrier and entering the systemic circulation via the mesentery.[99,100] Although the detailed changes in the gut microbiota of patients with severe burns have not been elucidated,[101,102] butyrate, a metabolite of gut bacteria, has been reported to promote Treg differentiation and suppress inflammation,[103] making intervention in the gut environment important in stabilizing immunity. Disruption of the bacterial flora in the intestinal tract is called dysbiosis,[104] and attempts such as symbiotic and fecal transplantation may be useful in curing this condition.[105]

CONCLUSIONS

Immunological changes after severe burn injury are reviewed from the acute to chronic phase. While many facts have been elucidated, no breakthrough treatment has been found, and treatment is likely to be similar to that in the general critically ill patient, along with proper supportive care. In particular, PIICS almost always occurs in patients with severe burns, which is why burns are called the king condition requiring intensive care.

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REFERENCES

1. Burns – World Health Organization (WHO), 2023.
2. Association AB. Practice guidelines collection. J Burn Care Res. https://academic.oup.com/jbcr/pages/practice_guidelines_collection. Accessed 07 May 2024.
3. The Japanese Society for Burn Injuries (JSBI) clinical practice guidelines for management of Burn Care (3rd Edition). Acute Med Surg 2022; 9(1): e739.
4. Association EB. European practice guidelines for burn care. 2017.
5. Committee IPG, Steering S, Advisory S. ISBI practice guidelines for burn care. Burns. 2016;42(5):953–1021.
6. Stanojcic M, Abdullahi A, Rehou S, Parousis A, Jeschke MG. Pathophysiological response to burn injury in adults. Ann Surg. 2018;267(3):576–84.
7. Pruitt B. The universal trauma model. Bull Am Coll Surg. 1985;70:2–13.
8. Huber-Lang M, Lambris JD, Ward PA. Innate immune responses to trauma. Nat Immunol. 2018;19(4):327–41.
9. Korkmaz HI, Flokstra G, Waasdorp M, Pijpe A, Papendorp SG, de Jong E, et al. The complexity of the post-burn immune response: an overview of the associated local and systemic complications. Cells. 2023;12(3):345.

10. Stoecklein VM, Osuka A, Lederer JA. Trauma equals danger—damage control by the immune system. J Leukoc Biol. 2012;92(3):539–51.
11. Osuka A, Ogura H, Ueyama M, Shimazu T, Lederer JA. Immune response to traumatic injury: harmony and discordance of immune system homeostasis. Acute Med Surg. 2014;1(2):63–9.
12. Ogura H, Hashiguchi N, Tanaka H, Koh T, Noborio M, Nakamori Y, et al. Long-term enhanced expression of heat shock proteins and decelerated apoptosis in polymorphonuclear leukocytes from major burn patients. J Burn Care Rehabil. 2002;23(2):103–9.
13. Hoover L, Bochicchio GV, Napolitano LM, Joshi M, Bochicchio K, Meyer W, et al. Systemic inflammatory response syndrome and nosocomial infection in trauma. J Trauma. 2006;61(2):310–7. discussion 316-7.
14. Sauaia A, Moore FA, Moore EE, Lezotte DC. Early risk factors for postinjury multiple organ failure. World J Surg. 1996;20(4):392–400.
15. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. 2012;72(6):1491–501.
16. Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. Nat Immunol. 2001;2(8):675–80.
17. Matzinger P. The danger model: a renewed sense of self. Science. 2002;296(5566):301–5.
18. Matzinger P. Tolerance, danger, and the extended family. Annu Rev Immunol. 1994;12:991–1045.
19. Manson J, Thiemermann C, Brohi K. Trauma alarmins as activators of damage-induced inflammation. Br J Surg. 2012;99(Suppl 1):12–20.
20. Relja B, Land WG. Damage-associated molecular patterns in trauma. Eur J Trauma Emerg Surg. 2020;46(4):751–75.
21. Jeschke MG, van Baar ME, Choudhry MA, Chung KK, Gibran NS, Logsetty S. Burn injury. Nat Rev Dis Primers. 2020;6(1):11.
22. Rani M, Nicholson SE, Zhang Q, Schwacha MG. Damage-associated molecular patterns (DAMPs) released after burn are associated with inflammation and monocyte activation. Burns. 2017;43(2):297–303.
23. Comish PB, Carlson D, Kang R, Tang D. Damage-associated molecular patterns and the systemic immune consequences of severe thermal injury. J Immunol. 2020;205(5):1189–97.
24. D'Alessio FR, Kurzhagen JT, Rabb H. Reparative T lymphocytes in organ injury. J Clin Invest. 2019;129(7):2608–18.
25. Xiao W, Mindrinos MN, Seok J, Cuschieri J, Cuenca AG, Gao H, et al. A genomic storm in critically injured humans. J Exp Med. 2011;208(13):2581–90.
26. Pantalone D, Bergamini C, Martellucci J, Alemanno G, Bruscino A, Maltinti G, et al. The role of DAMPS in burns and hemorrhagic shock immune response: pathophysiology and clinical issues. Review Int J Mol Sci. 2021;22(13):7020.
27. Greenhalgh DG. Management of Burns. N Engl J Med. 2019;380(24):2349–59.
28. Vourc'h M, Roquilly A, Asehnoune K. Trauma-induced damage-associated molecular patterns-mediated remote organ injury and immunosuppression in the acutely ill patient. Front Immunol. 2018;9:1330.
29. Rai V, Mathews G, Agrawal DK. Translational and clinical significance of DAMPs, PAMPs, and PRRs in trauma-induced inflammation. Arch Clin Biomed Res. 2022;6(5):673–85.
30. Iyer SS, Pulskens WP, Sadler JJ, Butter LM, Teske GJ, Ulland TK, et al. Necrotic cells trigger a sterile inflammatory response through the Nlrp3 inflammasome. Proc Natl Acad Sci USA. 2009;106(48):20388–93.
31. Collins LV, Hajizadeh S, Holme E, Jonsson IM, Tarkowski A. Endogenously oxidized mitochondrial DNA induces in vivo and in vitro inflammatory responses. J Leukoc Biol. 2004;75(6):995–1000.
32. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature. 2010;464(7285):104–7.
33. Billiar TR, Vodovotz Y. Time for trauma immunology. PLoS Med. 2017;14(7):e1002342.
34. Cekic C, Linden J. Purinergic regulation of the immune system. Nat Rev Immunol. 2016;16(3):177–92.
35. Asehnoune K, Roquilly A, Abraham E. Innate immune dysfunction in trauma patients: from pathophysiology to treatment. Anesthesiology. 2012;117(2):411–6.
36. Krzyzaniak M, Cheadle G, Peterson C, Loomis W, Putnam J, Wolf P, et al. Burn-induced acute lung injury requires a functional toll-like receptor 4. Shock. 2011;36(1):24–9.
37. Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, Lam HC, et al. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol. 2011;12(3):222–30.
38. Broz P, Dixit VM. Inflammasomes: mechanism of assembly, regulation and signalling. Nat Rev Immunol. 2016;16(7):407–20.
39. Stanojcic M, Chen P, Harrison RA, Wang V, Antonyshyn J, Zúñiga-Pflücker JC, et al. Leukocyte infiltration and activation of the NLRP3 inflammasome in white adipose tissue following thermal injury. Crit Care Med. 2014;42(6):1357–64.
40. Osuka A, Hanschen M, Stoecklein V, Lederer JA. A protective role for inflammasome activation following injury. Shock. 2012;37(1):47–55.
41. Ni Choileain N, MacConmara M, Zang Y, Murphy TJ, Mannick JA, Lederer JA. Enhanced regulatory T cell activity is an element of the host response to injury. J Immunol. 2006;176(1):225–36.
42. Delano MJ, Scumpia PO, Weinstein JS, Coco D, Nagaraj S, Kelly-Scumpia KM, et al. MyD88-dependent expansion of an immature GR-1(+)CD11b(+) population induces T cell suppression and Th2 polarization in sepsis. J Exp Med. 2007;204(6):1463–74.
43. Hotchkiss RS, Nicholson DW. Apoptosis and caspases regulate death and inflammation in sepsis. Nat Rev Immunol. 2006;6(11):813–22.
44. Zhang J, La X, Fan L, Li P, Yu Y, Huang Y, et al. Immunosuppressive effects of mesenchymal stem cell transplantation in rat burn models. Int J Clin Exp Pathol. 2015;8(5):5129–36.
45. Nemeth K, Leelahavanichkul A, Yuen PS, Mayer B, Parmelee A, Doi K, et al. Bone marrow stromal cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. Nat Med. 2009;15(1):42–9.
46. Minei JP, Cuschieri J, Sperry J, Moore EE, West MA, Harbrecht BG, et al. The changing pattern and implications of multiple organ failure after blunt injury with hemorrhagic shock. Crit Care Med. 2012;40(4):1129–35.
47. Bandyopadhyay G, De A, Laudanski K, Li F, Lentz C, Bankey P, et al. Negative signaling contributes to T-cell anergy in trauma patients. Crit Care Med. 2007;35(3):794–801.
48. Muire PJ, Schwacha MG, Wenke JC. Systemic T cell exhaustion dynamics is linked to early high mobility group box protein 1 (HMGB1) driven hyper-inflammation in a polytrauma rat model. Cells. 2021;10(7):1646.
49. Gosain A, Gamelli RL. A primer in cytokines. J Burn Care Rehabil. 2005;26(1):7–12.
50. Rendon JL, Choudhry MA. Th17 cells: critical mediators of host responses to burn injury and sepsis. J Leukoc Biol. 2012;92(3):529–38.
51. MacConmara MP, Tajima G, O'Leary F, Delisle AJ, McKenna A, Stallwood CG, et al. Regulatory T cells suppress antigen-driven CD4 T cell reactivity following injury. J Leukoc Biol. 2011;89(1):137–47.
52. Hanschen M, Tajima G, O'Leary F, Ikeda K, Lederer JA. Injury induces early activation of T-cell receptor signaling pathways in CD4+ regulatory T cells. Shock. 2011;35(3):252–7.
53. Wu D, Zhou M, Li L, Leng X, Zhang Z, Wang N, et al. Time series analysis of gene changes and processes after burn with human gene expression profiles. Burns. 2019;45(2):387–97.
54. Wu D, Zhou M, Li L, Leng X, Zhang Z, Wang N, et al. Severe burn injury progression and phasic changes of gene expression in mouse model. Inflammation. 2019;42(4):1239–51.
55. Dreckmann SC, Amini-Nik S, Tompkins RG, Vojvodic M, Jeschke MG. Genome-wide comparisons of gene expression in adult versus elderly burn patients. PLoS One. 2019;14(12):e0226425.
56. Wang P, Zhang Z, Yin B, Li J, Xialin C, Lian W, et al. Identifying changes in immune cells and constructing prognostic models using immune-related genes in post-burn immunosuppression. PeerJ. 2022;10:e12680.

57. Onishi S, Matsumoto H, Sugihara F, Ebihara T, Matsuura H, Osuka A, et al. Combination of HBA1, TTR, and SERPINF2 in plasma defines phenotype correlated with severe burn outcome. iScience. 2023;26(8):107271.
58. Hawkins RB, Raymond SL, Stortz JA, Horiguchi H, Brakenridge SC, Gardner A, et al. Chronic critical illness and the persistent inflammation, immunosuppression, and catabolism syndrome. Front Immunol. 2018;9:1511.
59. Chesney JA, Mitchell RA, Yaddanapudi K. Myeloid-derived suppressor cells-a new therapeutic target to overcome resistance to cancer immunotherapy. J Leukoc Biol. 2017;102(3):727–40.
60. Goldszmid RS, Dzutsev A, Trinchieri G. Host immune response to infection and cancer: unexpected commonalities. Cell Host Microbe. 2014;15(3):295–305.
61. Zhou J, Nefedova Y, Lei A, Gabrilovich D. Neutrophils and PMN-MDSC: their biological role and interaction with stromal cells. Semin Immunol. 2018;35:19–28.
62. Jeschke MG, Gauglitz GG, Kulp GA, Finnerty CC, Williams FN, Kraft R, et al. Long-term persistance of the pathophysiologic response to severe burn injury. PLoS One. 2011;6(7):e21245.
63. Hart DW, Wolf SE, Mlcak R, Chinkes DL, Ramzy PI, Obeng MK, et al. Persistence of muscle catabolism after severe burn. Surgery. 2000;128(2):312–9.
64. Ruhrmann S, Schneck E, Markmann M, Zink J, Zajonz TS, Arens C, et al. Trauma-induced Long-term alterations of human T cells and monocytes-results of an explorative, cross-sectional study. Shock. 2020;53(1):35–42.
65. Prescott HC, Angus DC. Enhancing recovery from sepsis: a review. JAMA. 2018;319(1):62–75.
66. Yende S, Kellum JA, Talisa VB, Peck Palmer OM, Chang CCH, Filbin MR, et al. Long-term host immune response trajectories among hospitalized patients with sepsis. JAMA Netw Open. 2019;2(8):e198686.
67. Ginde AA, Blatchford PJ, Trzeciak S, Hollander JE, Birkhahn R, Otero R, et al. Age-related differences in biomarkers of acute inflammation during hospitalization for sepsis. Shock. 2014;42(2):99–107.
68. Osuka A, Ishihara T, Shimizu K, Shintani A, Ogura H, Ueyama M. Natural kinetics of blood cells following major burn: impact of early decreases in white blood cells and platelets as prognostic markers of mortality. Burns. 2019;45(8):1901–7.
69. Semple JW, Italiano JE Jr, Freedman J. Platelets and the immune continuum. Nat Rev Immunol. 2011;11(4):264–74.
70. Smyth SS, McEver RP, Weyrich AS, Morrell CN, Hoffman MR, Arepally GM, et al. Platelet functions beyond hemostasis. J Thromb Haemost. 2009;7(11):1759–66.
71. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. Nat Rev Immunol. 2013;13(1):34–45.
72. Luker JN, Vigiola Cruz M, Carney BC, Day A, Moffatt LT, Johnson LS, et al. Shedding of the endothelial glycocalyx is quantitatively proportional to burn injury severity. Ann Burns Fire Disasters. 2018;31(1):17–22.
73. Basas VA, Schutzman LM, Brown IE. Implications of the regulation of endothelial glycocalyx breakdown and reconstitution in severe burn injury. J Surg Res. 2023;286:110–7.
74. Osuka A, Kusuki H, Yoneda K, Matsuura H, Matsumoto H, Ogura H, et al. Glycocalyx shedding is enhanced by age and correlates with increased fluid requirement in patients with major burns. Shock. 2018;50(1):60–5.
75. Hellenthal KEM, Brabenec L, Wagner NM. Regulation and dysregulation of endothelial permeability during systemic inflammation. Cells. 2022;11(12):1935.
76. Henneke P, Golenbock DT. Innate immune recognition of lipopolysaccharide by endothelial cells. Crit Care Med. 2002;30(5 Suppl):S207–S213.
77. Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. Blood. 2003;101(10):3765–77.
78. Frame JD, Eve MD, Hackett ME, Dowsett EG, Brain AN, Gault DT, et al. The toxic shock syndrome in burned children. Burns Incl Therm Inj. 1985;11(4):234–41.
79. McAllister RM, Mercer NS, Morgan BD, Sanders R. Early diagnosis of staphylococcal toxaemia in burned children. Burns. 1993;19(1):22–5.
80. Young AE, Thornton KL. Toxic shock syndrome in burns: diagnosis and management. Arch Dis Child Educ Pract Ed. 2007;92(4):ep97-100.
81. Gottlieb M, Long B, Koyfman A. The evaluation and Management of Toxic Shock Syndrome in the emergency department: a review of the literature. J Emerg Med. 2018;54(6):807–14.
82. Centers for Disease C. Toxic-shock syndrome—United States, 1970–1980. MMWR Morb Mortal Wkly Rep. 1981;30(3):25–33.
83. Llewelyn M, Cohen J. Superantigens: microbial agents that corrupt immunity. Lancet Infect Dis. 2002;2(3):156–62.
84. Matsushima A, Kuroki Y, Nakajima S, Sakai T, Kojima H, Ueyama M. Low level of TSST-1 antibody in burn patients with toxic shock syndrome caused by methicillin-resistant Staphylococcus aureus. J Burn Care Res. 2015;36(3):e120-4.
85. Matsushima A, Kuroki Y, Nakajima S, Kojima H, Seki T, Ueyama M. The incidence of toxic shock syndrome due to nosocomial methicillin-resistant Staphylococcus aureus infection in burn patients: a four-year retrospective cohort study. Burns. 2021;47(2):402–7.
86. Belba MK, Petrela EY, Belba AG. Epidemiology and outcome analysis of sepsis and organ dysfunction/failure after burns. Burns. 2017;43(6):1335–47.
87. Sharma BR, Harish D, Singh VP, Bangar S. Septicemia as a cause of death in burns: an autopsy study. Burns. 2006;32(5):545–9.
88. Liu X, Chen Y, You B, Peng Y, Chen Y, Yang Z, et al. Molecular mechanism mediating enteric bacterial translocation after severe burn: the role of cystic fibrosis transmembrane conductance regulator. Burns. Dent Traumatol. 2020;9:tkaa042.
89. Osuka A, Kusuki H, Matsuura H, Shimizu K, Ogura H, Ueyama M. Acute intestinal damage following severe burn correlates with the development of multiple organ dysfunction syndrome: a prospective cohort study. Burns. 2017;43(4):824–9.
90. Greenhalgh DG, Hill DM, Burmeister DM, Gus EI, Cleland H, Padiglione A, et al. Surviving sepsis after burn campaign. Burns. 2023;49(7):1487–524.
91. Steinvall I, Fredrikson M, Bak Z, Sjoberg F. Incidence of early burn-induced effects on liver function as reflected by the plasma disappearance rate of indocyanine green: a prospective descriptive cohort study. Burns. 2012;38(2):214–24.
92. Barret JP, Jeschke MG, Herndon DN. Fatty infiltration of the liver in severely burned pediatric patients: autopsy findings and clinical implications. J Trauma. 2001;51(4):736–9.
93. Jeschke MG, Barrow RE, Herndon DN. Extended hypermetabolic response of the liver in severely burned pediatric patients. Arch Surg. 2004;139(6):641–7.
94. Tapking C, Kilian K, Hundeshagen G, Haug V, Teufel A, Houschyar KS, et al. Hepatic functional pathophysiology and morphological damage following severe burns: a systematic review and meta-analysis. J Burn Care Res. 2022;43(5):1074–80.
95. Kirksey TD, Moncrief JA, Pruitt BA Jr, O'Neill JA Jr. Gastrointestinal complications in burns. Am J Surg. 1968;116(5):627–33.
96. Moore LJ, Patel S, Kowal-Vern A, Latenser BA. Cecal perforation in thermal injury: case report and review of the literature. J Burn Care Rehabil. 2002;23(6):371–4.
97. Muschitz GK, Fochtmann A, Keck M, Ihra GC, Mittlböck M, Lang S, et al. Non-occlusive mesenteric ischaemia: the prevalent cause of gastrointestinal infarction in patients with severe burn injuries. Injury. 2015;46(1):124–30.
98. Magnotti LJ, Deitch EA. Burns, bacterial translocation, gut barrier function, and failure. J Burn Care Rehabil. 2005;26(5):383–91.
99. Earley ZM, Akhtar S, Green SJ, Naqib A, Khan O, Cannon AR, et al. Burn injury alters the intestinal microbiome and increases gut permeability and bacterial translocation. PLoS One. 2015;10(7):e0129996.
100. Maejima K, Deitch EA, Berg RD. Bacterial translocation from the gastrointestinal tracts of rats receiving thermal injury. Infect Immun. 1984;43(1):6–10.

101. Feng Y, Huang Y, Wang Y, Wang P, Wang F. Severe burn injury alters intestinal microbiota composition and impairs intestinal barrier in mice. Burns Trauma. 2019;7:20.
102. Shimizu K, Ogura H, Asahara T, Nomoto K, Matsushima A, Hayakawa K, et al. Gut microbiota and environment in patients with major burns – a preliminary report. Burns. 2015;41(3):e28–e33.
103. Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature. 2013;504(7480):446–50.
104. Levy M, Kolodziejczyk AA, Thaiss CA, Elinav E. Dysbiosis and the immune system. Nat Rev Immunol. 2017;17(4):219–32.
105. Huang Z, Huang Y, Chen J, Tang Z, Chen Y, Liu H, et al. The role and therapeutic potential of gut microbiome in severe burn. Front Cell Infect Microbiol. 2022;12:974259.

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