

# Sepsis after trauma—evolving paradigms in stress biology and host response failure

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## Abstract

Severe trauma is often complicated by subsequent infection and organ dysfunction, with sepsis being a major mortality risk factor. Factors such as barrier destruction, wound contamination, invasive procedures, injury severity, and shock were traditionally considered primary predisposing elements for post-trauma sepsis. However, recent advances in stress biology have revealed a more nuanced understanding of the body's response to trauma. Organisms have evolved adaptive responses to various noxious stimuli that follow a biphasic pattern: Low to moderate stress levels can increase resilience, while overwhelming insults, both acute and chronic, overstrain the body's coping mechanisms and are known as allostatic overload, hallmarked by maladaptive responses. An illustrative example of this concept is the body's response to iron ion exposure following trauma, transfusion, or haemolysis. Iron ions, at low levels, induce adaptive Nrf2-dependent responses, such as haem oxygenase gene expression. However, high concentrations or prolonged exposure can lead to cellular damage and organ failure, e.g. through the production of highly reactive free radicals. This biphasic pattern highlights the complex interplay between protective and harmful responses in post-trauma physiology. Whereas tools such as the SOFA score allow to measure severity of organ dysfunction, no metrics for quantifying the intensity of 'stress' over time are available. As cumulative stress is a crucial outcome-associated factor in trauma care, the development of adequate indicators could significantly enhance our understanding and management of post-trauma complications, arising from secondary surgical interventions, transfusion management, or metabolic derangements. This evolving perspective on stress biology in the severely injured host underscores the need for a more comprehensive approach to patient assessment and treatment in critical care settings, to identify and to decrease stress load with the aim to prevent life-threatening complications, such as sepsis, and ultimately improve outcomes.

**Keywords:** Trauma; Infection; Organ dysfunction; Stress; Holobiont; Allostatic load; Resilience

## Highlights

- Understanding of the host response to trauma is currently changing with the recognition of the human host as a 'holobiont', advancing earlier concepts of the gut as 'source and motor' of multi-organ dysfunction in severe trauma.
- Divergent inflammatory phenotypes, such as 'hyperinflammation' or 'immunoparalysis' have been described in trauma and sepsis replacing the former concept of 'systemic inflammatory response syndrome' as a stereotypic damaging mechanism.
- More recent insights into stress biology suggest a need to consider aspects of dose responses or 'hormesis'. The host response to trauma and eventual subsequent infection should be interpreted as a biphasic rather than a linear, non-threshold damaging response.

## Background

Trauma patients in intensive care units (ICUs) face a significant risk of developing nosocomial sepsis [1]. However, distinguishing between a systemic inflammatory response to trauma and tissue damage, which is often accompanied by fever and leukocytosis, and infectious complications presents a considerable diagnostic challenge in critically ill patients. The signalling events leading to infection- and damage-associated activation of the innate immune response through Toll-like receptor ligands are well understood, with significant overlap between infection and trauma responses [2]. Despite this knowledge, the clinical dilemma persists, contributing to antibiotic overuse in modern ICUs. Ruling out infection in trauma patients is often difficult due to often similar presentation and multiple risk factors. These include not only penetrating trauma, altered barrier function, and

wound contamination but also complex immune dysfunction, particularly at the interface between host immune cells and the gut microbiome [3]. This creates a particularly challenging differential diagnosis in trauma and burn patients with shock and prolonged gut ischemia. The concept of gut-derived pathogens as a source of self-infection has been recognized for many decades. The role of the 'leaky gut' as the source of the 'septic' appearance in trauma patients has been a subject of intense debate in both literature and clinical practice [4]. Moreover, the similar host responses to damage-associated molecular patterns (DAMPs) released during trauma complicates the clear-cut diagnostic distinction (Figure 1).

This review aims to explore the conceptual progress in understanding the host response to trauma, infection, and general stress, with a particular focus on the evolving concepts

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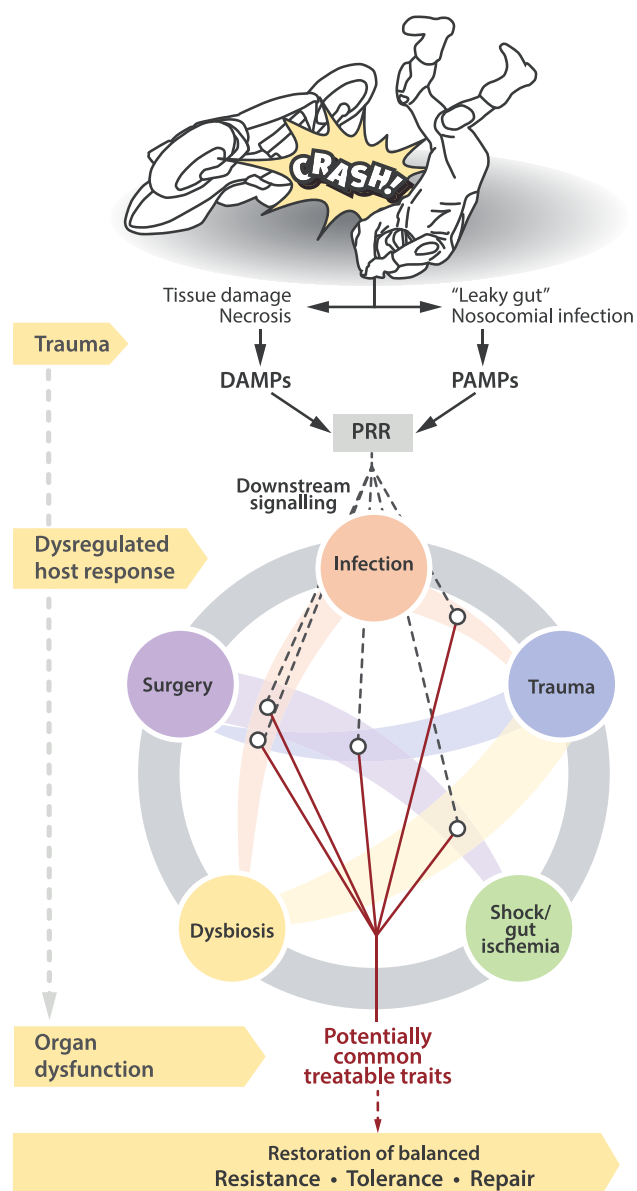


Figure 1. Identifying common treatable traits in the host response to trauma and infection. Complications from trauma and infections result from a dysregulated host response to the primary and/or subsequent insults. General stress response pathways intersect and thus might offer the opportunity to identify common treatable traits for different clinical conditions. Knowledge of these pathways can help to optimize timing of interventions and to develop therapies targeted to modulate the patients stress response, thereby restoring functional adaptive responses and improving patient recovery

of the biphasic nature of stress responses [5]. By examining these advances, we hope to shed light on the complex interplay between trauma, infection, and the body's stress response that can lead to 'resilient', 'tolerant', 'primed', or 'trained' phenotypes.

The objective of this narrative review is to evaluate the complex interplay between trauma, infection, and the body's stress response and the discussion of translation into the field of translational sepsis research including development of new strategies for diagnosis and treatment. A search in the main biomedical databases (PubMed, Medline, Scopus, and Web of science) was conducted for a 20-year period ending in

July 2023, focused on primary research articles in the field of interest. Keyword search for abstracts and titles included ('trauma' OR 'organ dysfunction') AND ('sepsis') AND ('host response'). The search identified 576 references, which were selected by particular importance for this review. The pre-screened references were completed by other publications related to the issue.

## Review

### From SIRS to current concepts of sepsis immunology—'inflammation', 'immune paralysis' and organ dysfunction as the hallmark of a maladaptive host response

More than three decades ago, Roger Bone and colleagues introduced the Systemic Inflammatory Response Syndrome (SIRS), which can be triggered by a broad variety of harmful stressors. In this concept, SIRS can occur in response to burns and trauma as well as in sepsis. The body's response is strikingly similar, including the development of multiple organ dysfunction syndrome; only the infectious trigger discriminates sepsis from the traumatic causes [6]. This, but also individual variability of the body's response, makes the identification of infectious complications in severely traumatized patients a challenge [7]. Strikingly, the SIRS criteria already included hints to opposing host responses, such as fever or hypothermia and elevated or reduced white blood cell counts. SIRS criteria are no longer used in specifying sepsis, which is now defined as a maladaptive host response to infection, hallmarked by organ dysfunction [8]. However, divergent aberrances of white blood cell counts already forbade a subsequent conceptual leap, which proposed that the immune system's response could be exaggerated ('pro-inflammatory'), dampened ('immunoparalytic'), or mixed [9] during life-threatening infection. The current model of sepsis immunology places pro-inflammatory and immunosuppressive categories at opposite 'poles' of the dysregulated host responses. Compelling evidence supports this notion, but consistent categorization between these extremes is still in progress and even for evident immunosuppression or hyperinflammation no successful immunomodulatory therapies have been established yet. Variable phenotypes have been identified through hypothesis-driven research, such as macrophage activation-like syndrome (MALS) [10] and interferon- $\gamma$ -driven sepsis (IDS) [11], as well as by data-driven approaches, such as the  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  phenotypes proposed by Seymour *et al.* [12].

Currently, promising clinical tests of immune-modulatory therapies based on these concepts are underway [13].

### Sequential stress and dose-response considerations in the host response

Treatment of severe trauma typically involves a sequence of stressful events including tissue damage, surgical interventions, and invasive procedures such as mechanical ventilation or parenteral nutrition. These stressors can alter cellular signalling cascades affecting immune responses both acutely, e.g. through MAP kinase effects, and over longer periods via epigenetic modifications. The effects on immunity have long been described as 'priming', 'training', or 'tolerance', with significant impacts on patient outcomes [14]. While 'endotoxin tolerance' is well-documented, priming responses

occur less frequently and are less obvious. A prominent example of maladaptive priming is the Sanarelli-Shwartzman reaction that can lead to haemorrhage, necrosis, and shock and organ failure upon repeated exposure to gram-negative bacteria [15]. This occurs through overwhelming of phagocytic cells, triggering hypercoagulability, and microvascular failure upon re-exposure. Likewise, various stress programmes, such as acute phase and heat shock responses, can profoundly alter susceptibility to subsequent insults, though they may be mutually exclusive leading to divergent states of altered responsiveness [16]. Only considering acute events in the assessment of the patient's stress status oversimplifies the problem by disregarding comorbidities and general health. The Injury Severity Score (ISS) is the most commonly used system for scoring patient injuries and prediction of morbidity and mortality [17]. While the ISS does not include the patient's age and comorbidity status, a retrospective analysis of 5000 Taiwanese patients showed an association of age and comorbidity index with higher ISS and longer hospital stay. Overall, in the multivariable analysis of transition-specific Cox models, comorbidities were associated with higher risk for hospital mortality and with lower probability of transition-to-discharge [18]. However, to predict whether a previous stressor such as trauma predisposed the host to increased susceptibility or induced tolerance/resilience is currently difficult to predict. However, the effects of sequential stress events may explain why surgical revisions in critically ill patients sometimes trigger unexpected deterioration of organ function. The prevailing paradigm suggests the underlying cellular alterations primarily manifest as maladaptive innate immune responses, contributing to infectious complications and sepsis. The role of nosocomial infections as a major trigger for secondary organ dysfunction in late-stage trauma is well-accepted, often leading to prolonged 'prophylactic' antibiotic use [19, 20]. This raises important questions about how various stressors interact in the overall stress response, potentially leading to cross-tolerance or priming phenomena. Specifically, how might trauma prime the body for organ dysfunction upon developing nosocomial infection, such as pneumonia? How does the timing of surgical revisions affect outcomes in critical illness? Understanding these complex interactions between different stressors and their impact on host physiology remains a crucial area for further research in trauma and critical care medicine, presumably requiring a tool to quantify a state of 'stress'. Numerous biomarkers and their combinations to quantify stress have been investigated for a long time (e.g. reviewed by [21]), but still no established tools for routine clinical application are available.

There are three dominating concepts regarding additive and sequential stress: Hormesis focuses on dose–response effects [22], allostasis introduces adaptation by change, as opposed to homeostasis, and stands out by integrating psychological elements of stress and their translation to physiological reactions [23]. Finally, the general adaptation syndrome focuses on overlapping pathophysiology resulting from different diseases or stressors [24]. A common notion of these concepts is a dose-dependent response to stress and hence a distinction of beneficial eustress and detrimental distress, in which the latter refers to prolonged and/or intense stress that overwhelms the organism's coping mechanisms. A particular trait of Selye's concept of the general adaptation syndrome is the inclusion of 'alarm reaction' upon an acutely stressful event. Although the mentioned concepts should best be viewed as complementary,

the alarm reaction might be of special interest in connection to physical trauma, which represents a sudden hit—but the consequences thereof are strongly influenced on the patients stress state before the trauma as well as stressors associated with medical care and recovery.

### Redefining the 'stress response' in the critically ill

The relationship between stress and susceptibility to complications in critical illness is complex. While increased vulnerability is often expected, the phenomenon adaptation, as included in all stress concepts outlined above, suggests that exposure to low doses of stressors can actually promote resilience and increase stress tolerance in organisms.

Hormesis has been observed in connection with diverse stressors pertinent to critical care, including heat, cold, food deprivation, and more recently, infection [25]. Whereas interactions with commensal microbes commonly are viewed as potentially beneficial, encounters with pathogens are considered universally detrimental. This linear, non-threshold model of pathogen interactions fails to explore potential fitness-promoting effects of pathogen exposure [25]. However, recent studies in model organisms and rodents support the concept of hormetic responses to infection, with non-lethal pathogen doses linked to beneficial adaptations, e.g. wound healing through mitochondrial oxidative stress responses, i.e. 'mitohormesis' [26]. These findings suggest a need to reassess the effects of pathogens on host fitness as a function of pathogen load and of the state of the stress response [25]. Additionally, this nuanced understanding challenges the liberal use of 'pre-emptive' or 'prophylactic' antibiotics, recognizing that disruption of the microbiome through antibiotic overuse may itself prime the host for maladaptive responses. In the context of burn and trauma patients, these stressors interact in complex ways, modulating the interplay between host cells and microbiota at damaged barriers and presumably in the gut.

Besides altered exposure to pathogens, exposure to iron ions changes drastically in trauma and sepsis development after multiple injuries and strong evidence exists for biphasic stress responses to exposure to iron ions [27, 28].

We will use exposure to microbiome/pathobiome as well as iron to illustrate stressor associated to trauma with the potential to alter outcome, but also offering perspectives for improved treatment options. Clinically, the ability to assess a patient's state of susceptibility or resilience could inform surgical planning and improve outcomes for vulnerable patients upon sequential stress [Table 1](#).

### Humans as 'holobionts'—understanding the role of the gut microbiome in trauma and sepsis

The term 'microbiome' refers to the entirety of microorganisms that colonize a living organism. This diverse community includes bacteria, fungi, and (less-studied) viruses that significantly outnumber the eukaryotic cells of the host. The majority of these microorganisms reside in the gut, where they play crucial roles, such as producing vitamins and controlling potential pathogens [29]. Due to the microbiome's importance, humans are often considered 'holobionts', i.e. a biological system comprising a eukaryotic host and a multitude of closely associated prokaryotic species. The microbiome is highly diverse, encompassing several thousand different species [30, 31]. Its role in regulating immunity has gained significant attention in the context of critical illness,

Table 1. Conceptual matrix of factors, challenges, and read outs for personalizing interventions in post-trauma sepsis

|                             | Tissue damage (Trauma/burn injury)                                                    | Host response                                                                                                                                                | Infection/sepsis                                  |
|-----------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Pathophysiological concepts |                                                                                       | Timing and response to treatment                                                                                                                             |                                                   |
|                             | Release of DAMPs/PAMPs [2]                                                            | Immune response/<br>Variable endotypes [11, 12]                                                                                                              | Release of PAMPs/DAMPs [2]                        |
|                             | Microcirculatory impairment [35]                                                      | Microbiome: modulation of immune response/impaired barrier function [34]                                                                                     | Microcirculatory impairment [35]                  |
|                             | Prolonged gut ischemia [35]                                                           | Diversity and composition of microbiome [36, 37]                                                                                                             | Prolonged gut ischemia [35]                       |
|                             | ‘Leaky gut’ [35]                                                                      | Dysbiosis [36, 37]<br>Barrier disruption [34–37]<br>Release of heme, iron ions, intercepting proteins as well as activation of detoxifying pathways [27, 69] | Antibiosis                                        |
| Read out                    | HPA, cortisol, (proteins of) iron metabolism, e.g ferritin, hepcidin [28, 43, 45, 60] | SOFA, HRV [61, 62, 67]                                                                                                                                       | e.g. procalcitonin                                |
| Challenges                  | (timing of) surgical interventions<br>impaired tissue regeneration                    | Allostatic overload [21, 51]                                                                                                                                 | Continuation of or<br>recovery from tissue injury |
|                             | Susceptibility to secondary infections [20]<br>Pre-emptive antibiosis [19, 20]        | Biphasic response (Hormesis) [5, 22, 25]                                                                                                                     | Susceptibility to secondary infections [33]       |
|                             | ↘                                                                                     | ↓                                                                                                                                                            | ↗                                                 |
| Aims & action               | Personalized interventions                                                            |                                                                                                                                                              |                                                   |

as altered immune function can lead to organ dysfunction, morbidity, and mortality. Interventions affecting the gut microbiome, such as the liberal use of antibiotics in ICUs, are of growing concern. Antibiotics not only contribute to the development of resistance at the community level but can also cause dysbiosis in individual patients, leading to increased morbidity and mortality [32]. On any given day, approximately twice as many ICU patients receive antibiotics than are suspected of having infections [33]. The impact of critical illness on the microbiome extends beyond antibiotics. Other ICU interventions, such as proton pump inhibitors and fasting, also affect human microbial habitats, often resulting in a marked decrease in microbial diversity. Dysbiosis, characterized by a significant loss of microbial diversity and pathogen overgrowth, is linked to organ dysfunction in critical illness, particularly in trauma and burn patients. In healthy individuals, the intestinal epithelium absorbs nutrients and prevents the translocation of gut flora, maintaining a barrier function. However, this barrier can be compromised by host factors such as shock or changes in the microbiota composition [34]. Both microbiota alterations and the development of a ‘leaky gut’, e.g. due to altered mesenteric perfusion can contribute to the gut becoming a source of self-infection [35]. This concept, dating back at least several decades, is gaining renewed attention with the advent of next-generation sequencing techniques allowing large-scale longitudinal studies into the hologenome. Recent studies indicate rapid microbiome changes upon traumatic injury [36] and reduced alpha diversity in both trauma and sepsis patients [37]. However, the specific dysbiotic signatures clearly differed between trauma and sepsis patients and female patients were more resilient to dysbiosis, coinciding with often better clinical outcomes [37]. As we will later discuss social stress as an important factor for overall resilience, it is worth

mentioning that social determinants of health have been suggested to influence microbiome composition and thereby— even before onset of acute disease—can alter probabilities of positive or adverse outcomes [38]. These advancements, along with improved data science, are enhancing our understanding of complex syndromes and personalized (pharmaco)-therapy [39]. Additionally, a deeper comprehension of the molecular mechanisms underlying organ dysfunction and the influence of microbiomes ‘ecological memory’ [38] will continue to reshape our understanding of stress biology in the context of infectious diseases.

Iron ions in trauma and sepsis: a double-edged sword

Iron ions are in almost all living organisms the most abundant transition metal participating in a wide range of metabolic processes [40]. The tight control of the potentially toxic free iron ions is required due to the catalytic capacity of iron ions for generation of reactive oxygen species (ROS) causing damage of proteins, lipids, and DNA [41]. With bleeding following trauma, degraded erythrocytes release massive amounts of iron-containing haemoglobin. Increased levels of free haem, iron ions, intercepting proteins and detoxifying pathways are hallmarks of trauma and associated with post-trauma sepsis (Figure 2) [28].

Chelating iron by binding to free pairs of electrons from sulphur, oxygen, or nitrogen atoms is preventing the generation of ROS and serves for detoxification in a broad range of proteins [41]. Since iron ions are also essential for the growth of pathogens, retaining iron availability to the host while restricting access to the pathogen is important and associated molecules, such as lactoferrin or ferritin, which serve as markers and mediators during the course of the disease [42–44]. Hepcidin is the master regulator of ferroportin, an

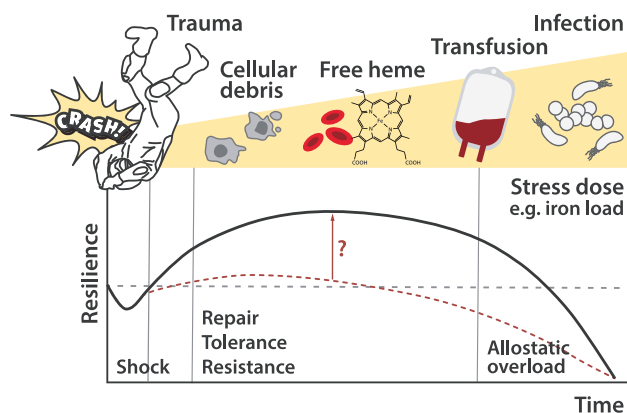


Figure 2. Host fitness as a function of stress dose. Stressors, such as heat, cold, fasting but also toxic compounds such as  $\text{Fe}^{2+/3+}$  ions typically have fitness-promoting effects at low dose while they impair host integrity at higher doses, a phenomenon termed hormesis. Response to trauma is often characterized by an initial shock phase and the subsequent events expose the patient to a variety of further stressors, e.g. exposure to  $\text{Fe}^{2+/3+}$ .

iron exporting protein suppressing the release of iron to the bloodstream from its reservoirs [27], distinguishing patients with severe infection from those with surgical trauma [45]. Hepcidin is also held responsible for ICU-common anaemia which in turn is associated with outcome [46, 47]. In a bioinformatics and network-topology-based approach studying the interplay of iron metabolism and immune function, close links were identified at different levels, including antigen presentation, catalyzing redox reactions, ubiquitination, endocytosis, and lysosomal degradation [48].

Given the central role of iron in the cellular energy metabolism, parameters of iron-modulating proteins might function as measures of stress and adaptation. Elevation of circulating free haem following trauma is positively associated with systemic inflammation but also transcriptional upregulation of the detoxifying enzyme hemoxygenase-1 (HO-1), e.g. in PBMC which reflects a central hallmark of the adaptive stress response [28, 49].

An increase of fragmented erythrocytes and (mass) transfusion following trauma serve as main sources of free haem, an important alarmin, and ligand to TLR receptors [28, 49]. Severe trauma induces a decrease of albumin and hemopexin during the initial phase [49], which impairs the host's ability to deal with iron overload. Accordingly, albumin was proposed not only as a predictor of mortality in ICU-patients with sepsis [50], but also as a measure of allostatic load [21, 51].

Albumin also carries the most abundant plasma thiol-pool directly detoxifying ROS and electrophiles [52, 53] and has a high affinity and capacity for binding of copper and iron ions, decreasing their availability for generation of ROS [22]. Iron- and copper-mediated hormetic effects have already been established in a broad range of diseases, most notably neurodegenerative disorders [54].

Haem and its degrading enzyme, haem oxygenase (HO-1), can be considered the most prominent stress sensors in surgical patients [49]. Induction of HO-1 may confer protection, e.g. by controlling intracellular levels of toxic haem, or by anti-inflammatory, anti-apoptotic, and blood flow-maintaining effects of its by-products biliverdin and carbon monoxide [55]. However, the protective action may be restricted to a rather narrow window of overexpression, reflecting a 'hormetic' pattern of action [56].

## Stress—beyond physiology

Stress, in particular in the frame of the allostasis concept, embraces social and psychological stress as important factors for the overall organismal response [57].

In line with this notion, the evolving understanding of the stress response in critical illness incorporates insights from both biomedical and social sciences. Social sciences have also developed methods to measure and compare stress responses over decades, providing potential frameworks for application in critical care. This evolving perspective on stress responses in critical illness highlights the need for more nuanced approaches to patient care, recognizing both the potential benefits and threats of controlled stress exposure.

Social sciences have contributed significantly to understanding and coping with stress, emphasizing the role of social support in resilience. Studies show that positive social support can enhance resilience to stress, help protect against developing trauma-related psychopathology, and reduce morbidity and mortality. The redefinition of stress response in critical illness emphasizes the need for an interdisciplinary approach, integrating insights from biomedical sciences, psychology, and social sciences to develop comprehensive strategies for patient care [58, 59].

Cortisol levels, measured from saliva, blood, or hair samples, provide insight into the activation of the hypothalamic-pituitary-adrenal (HPA) axis, a key component of the physiological stress response [60]. Complementing this, heart rate variability (HRV) serves as a valuable indicator of autonomic nervous system function, with lower HRV typically associated with higher stress levels [61, 62]. The advent of wearable devices and mobile applications has further enhanced our ability to monitor stress responses in real-time, tracking physiological markers such as heart rate, skin conductance, and activity levels continuously even in the post-acute care of critical illness [63]. These technological advancements have paved the way for ecological momentary assessment (EMA), a method that involves repeated sampling of individuals' behaviours and experiences in their natural environments using mobile devices [64].

Concepts of stress response in social sciences highlight the complexity and variability of stress at both individual and community levels. Frameworks, such as allostatic load and hormesis, provide a deeper understanding of how stress impacts health and well-being. Integrating these frameworks and measurement techniques, such as self-report scales, into critical care settings might enhance our understanding of stress in critically ill patients. An interdisciplinary approach, combining insights from social sciences and biomedical research, holds promise for improving outcomes in critical care and post intensive care syndrome.

The study of stress response and resilience reveals a complex interplay between biological, psychological, and social factors [65]. The dynamic nature of resilience presents both challenges and opportunities in identifying at-risk patients and tailoring interventions. Social sciences employ a range of tools including self-report measures, behavioural coding, and physiological assessments such as cortisol levels and HRV. In contrast, critical care medicine relies heavily on biomarkers and scoring systems, most notably the SOFA score [66–68]. Interdisciplinary approaches applying complementary insights to patient care, could allow exploring ways to personalize interventions based on individual stress responses and resilience profiles. An interdisciplinary approach would

reflect a growing recognition of the complex, dynamic nature of stress responses and resilience, driving the development of more nuanced frameworks and measurement approaches to capture this complexity effectively.

## Conclusions

This evolving perspective on stress response in critical illness underscores the complexity of human responses to severe stressors and the importance of considering both biological and psychosocial factors in patient care. It suggests that effective management of critically ill patients requires a holistic approach that addresses not only physiological parameters but also psychological and social aspects of stress and resilience. From a merely biomedical point of view, the concept of common molecular pathways mediating stress responses might lead to the identification of treatable traits that may equally benefit critically ill patients suffering from different conditions and may enable prevention of complications by targeted modulation of the stress response.

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## Author contributions

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## Conflict of interest

The authors declare that this review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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