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The stressed host response to infection: the disruptive signals and rhythms of systemic inflammation

Stephen F. Lowry, M.D., F.A.C.S., F.R.C.S.(Ed)(Hon) [Professor and Chair]

Department of Surgery, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, N.J. 08901

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Recent surveys document an increasing incidence of community-acquired and nosocomial infections in the United States, with a significant proportion of these infections occurring in an increasingly aged population with underlying health problems^{1,2}. Among surgical patients, the stresses of operation or injury also increase the risks for infection and solid organ dysfunction across all population demographics³. The present incidence of acquired infection approximating 2–3% will very likely continue to increase among non-trauma, surgical patients⁴.

The stressed clinical phenotype

The manifestation of systemic inflammatory response syndrome (SIRS) criteria is the common clinical phenotype of stressed, surgical patients. Concerns have repeatedly been expressed that SIRS lacks sufficient specificity and prognostic value since the time the concept was originally proposed as a mechanistically-based risk stratification system.^{5,6} The SIRS concept does retain value within surgical populations where morbidity and mortality risks are correlated to the expression and duration of SIRS^{7,8,9}.

In essence, the SIRS phenotype, reflects the presence of consequential systemic inflammation and suggests increasing risk of complication and adverse outcome if the criteria are manifested over an extended period. The initial inflammatory stimulus for SIRS may arise from any number of etiologies, including “sterile” stresses, such as pancreatitis or cross-sectional tissue injury resulting from involuntary injury or surgical interventions. These injuries incite autonomic nervous and neuro-endocrine signals that induce limited SIRS criteria, such as leukocytosis^{10,11} and increased heart rate, but the simultaneous presence of three or more SIRS criteria is infrequent without overt activation of the innate immune system. It remains to be determined whether this activation can arise solely from “sterile” signals such as injured tissues or, in many cases, really signifies activation via undetected endogenous or exogenous pathogen ligands¹².

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Corresponding author and reprints: Stephen F. Lowry, M.D., Department of Surgery, Robert Wood Johnson Medical School, 125 Paterson Street, Suite 7300, New Brunswick, N.J. 08901, Phone: (732) 235-6096, FAX: (732) 235-6003, Email: E-mail: lowrysf@umdnj.edu.

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Evolution did not anticipate the successes of current surgical care or exogenous resuscitation/organ system support and antimicrobial therapies. Many mechanisms of the host response to localized and systemic inflammation have been defined at the molecular level and recent summaries of these insights relevant to surgical patients have been published^{13–16}. We are also increasingly aware of important endogenous variables unique to the individual host. These include, among others, the problems of confounding conditions/treatments and ageing influences as well as less overt influences arising from genetic variation. Each of these components contributes to variability in the expressed phenotype of individual patients. In this review, some insights from molecular investigations of inflammatory processes will be discussed in the context of host-specific factors and clinical management practices in surgical patients with an acquired infection. The discussion briefly outlines conserved innate immune and neuro-endocrine system responses that may transiently restore destabilizing insults.

Acute stressful conditions often precede the secondary insult of pathogen invasion in surgical patients. As a consequence, the so-called “two-hit” model of inflammatory insult has become the commonly accepted paradigm for stressful injury. We are cognizant that the second “hit” may be “sterile” or pathogen induced in nature. Although the secondary insult in the context of SIRS is generally perceived to occur one or more days after the initial insult, some have suggested that a demonstrable secondary host response may be elicited within a matter of hours after the initial traumatic event⁹. Most prevailing models of secondary insult disregard the role of unknown variables in considering how intrinsic regulatory signals, as well as pathogen virulence, interact during ongoing stress. The discussions below address the question as to how an existing, non-pathogen induced stress receives signals from both endogenous (patient specific) and exogenous (treatment or pathogen) influences that modify the phenotypes and outcomes of an acquired infection.

Local inflammatory signals

In mounting a defense against invasion by foreign organisms, the innate immune responses may well destroy both injured and normal tissues and delay processes of wound repair and resolution of inflammation. To facilitate this immune activation, escalation, and resolution, Nathan has described a “go-no go” binary information flow amongst immune cells and injured tissues as a necessary command/control system. The reader is referred to his outstanding discussions for greater detail.^{17,18} Tissue molecular signals directing the resolution of localized inflammation are also programmed at an early juncture¹⁹ although the regulation of these processes during systemic inflammatory conditions is unclear. Contemporary injury science is seeking to define how host recognition systems distinguish and differentially respond to the states of sterile and non-sterile insult.

The immune response to tissue damage must propagate this information within the injury site against a background of systemic inflammatory responses (SIRS) that has potential to disrupt this controlled information exchange and cellular reprogramming²⁰. A significant injury focus is not isolated from systemic, endogenous signals that modulate tissue blood flow, cellular metabolism, and what are early containment enforcing, anti-inflammatory signals. The host receives input signals regarding the status of the injury site(s) via a combination of soluble and “hard-wired” information channels. This bi-directional information exchange is conveyed by several classes of soluble mediators as well as by direct neural tissue sensing of mediators at local sites^{21–24}.

THE RESPONSE TO THE INITIAL INSULT

Manifestations of the initial insult

There may be little evidence of a systemic response in subjects with mild or modest injury³. An insult of sufficient magnitude to induce several SIRS criteria will induce systemic responses that encompass many features of a pro-inflammatory state, including activation of the coagulation and complement cascades, as well as leukocyte and endothelial cell activation. Munford and Pughin²³ have discussed the temporal dynamics of this initial pro-inflammatory systemic response that evolves in short order to become anti-inflammatory in nature.

The neuroendocrine response

Activation of the hypothalamic-pituitary-adrenal axis (HPA) is the classic neuro-endocrine response to stressors, including sterile tissue injury, hypoperfusion, or pathogen invasion^{25, 26}. In a previously healthy host, the initial injury-induced HPA activation elicits a hypermetabolic response and serves to acutely maintain hemodynamic stability, facilitate reprogramming of acute phase proteins, and exert anti-inflammatory activity. Importantly, HPA activation also promotes an early systemic, net anti-inflammatory signal as reflected in reduced levels of several pro-inflammatory mediators and/or priming of immune cells for production of anti-inflammatory molecules, such as IL-10.¹¹ However, the duration of these HPA-induced anti-inflammatory signals appears to be limited and probably dissipates within a few hours to days after the initial insult.^{10,11}

Neuroendocrine system activation also includes several recently identified peptides that may act in parallel to HPA derived signals and serve as bridging signals to adaptive immune generation.²⁷ These anti-inflammatory peptides act, in part, via the cAMP-PKA signaling pathway and are inducible by infectious ligands. The durability of signaling via these neuropeptides in the context of ongoing, severe inflammation is largely unknown but they may serve as an alternative anti-inflammatory mechanism as the influence of other HPA derived signals wane.

Signals for innate immune system activation—As noted above, the innate immune system is initially activated at the local tissue injury site. Resident cells initiate this response and amplify signals for further recruitment of neutrophils and macrophages. These cells express cell surface pattern-recognition receptors (PRRs) that detect invariant, conserved molecular patterns and foreign nucleic acid structures allowing the detection of the wide range of microbial pathogens. There are several PRR families that have been identified²⁸ as signal transducers for threatening exogenous (extra- and intracellular pathogen) molecules and endogenous (non-viable or injured tissue) products. The well-described Toll-like receptors serving these functions also interact with more recently defined intracellular signaling molecules, such as (NOD)-like receptors (NLRs) and a multiprotein cellular complex (inflammasome) that activates cellular caspases²⁹. These later mechanisms lend potential breadth and intensity to the innate inflammatory repertoire although, again, the activity of NLRs and the inflammasome pathways have not been well described during conditions of sustained stress.^{30,31}

During conditions of sterile injury, the cognate ligands for PRRs include diverse products of disrupted cells, including, among others, heat shock proteins, mitochondrial peptides bearing the N-formyl group motif, hyaluronan, uric acid, and the transcription factor HMGB1.^{17,18, 30,31} The Toll-family receptors are increasingly implicated as receptors for these ligands.^{29, 32}

In many cases the early systemic responses to “sterile” injury are indistinguishable from those arising from infection and many of the same cellular activation events are observed³³. This is not surprising given that signals derived from both tissue injury and infection converge on the same receptors. Hence, a major consideration is how the immune system recognizes such non-pathogen-induced signals²⁹ and provides informational cues that constrain the more damaging inflammatory responses invoked by microbial invasion¹⁷.

Rhythms after the first hit

Homeostasis exhibits rhythmic physiological and biochemical activities. The temporal predictability of this endogenous control is presumed to confer acute adaptive advantages³⁴ that very likely extend to modulating systemic illnesses and solid organ function³⁵ over extended periods.

Circadian entrainment—The molecular regulatory components of the circadian clock³⁶ generates synchronization that co-ordinates phase relationships among numerous internal rhythms³⁷. Indeed, many gene products of the core circadian clock are embedded in regulatory networks necessary for normal cell function³⁸. During health, circadian rhythms entrained by light/dark and food intake cycles are readily detectable as neuro-endocrine secretory and autonomic activities, including heart rate and blood pressure.

As will be discussed below, these entrainment cues are frequently altered in stressed, hospitalized patients and the consequences of this loss of environmental cues have yet to be fully defined in the context of stress³⁹. Recent data document that inflammation-inducing ligands, including endotoxin⁴⁰ and TNF α ⁴¹, suppress the expression of clock regulatory genes in the suprachiasmatic nucleus and in peripheral tissues. This linkage of innate immune system activation to circadian rhythm control has yet to be explored in the setting of persistent systemic inflammation.

Autonomic rhythms—Autonomic function also exhibits circadian rhythmicity as assessed by measures of heart rate variability (HRV),⁴². This daily fluctuation in both frequency and power spectra has implications for sympathetic and parasympathetic balance and the acute regulation of systemic inflammatory activity. Autonomic imbalance, reflected by sympathetic activity excess (or parasympathetic attenuation) is associated with increased morbidity in patients with severe sepsis⁴³. A reduction in parasympathetic activity may be associated with diminished capacity to exert vagal, cholinergic control over pro-inflammatory mediator activity⁴⁴. Reductions in implied vagal nerve activity have now been noted during inflammatory conditions associated with endotoxemic conditions in humans⁴⁵ and in experimental conditions of sterile systemic inflammation⁴⁶. Hence, continued attenuation of vagal activity during SIRS may impede this alternative mechanism for controlling inflammatory balance.

Endocrine rhythms—The secretion of endocrine hormones are also subject to circadian rhythms as well as intermittent stimuli such as feeding and emotion⁴⁷. As detailed elsewhere, a characteristically enhanced endocrine hormone profile is elicited during the early phase response to injury or infection^{18,26,48,49}. These hormone signals promote acute phase metabolic and immunologic programming of target tissues.

Pathogens of the initial insult

Comprehensive discussions of the spectrum of initial pathogens complicating surgical illnesses are provided elsewhere in this volume. The reader is also referred to recent overviews of pathogen recognition mechanisms and discussion of virulence acquisition^{28,29,50} as well as discussions of plausible genetic determinants of pathogen recognition and immune

responsiveness^{51–53}. Most such reports do not, however, discuss these factors in the context of an existing non-pathogen induced host responses.

Modifiers of the initial injury response

A healthy person subjected to an acute insult relies upon the above stereotypic responses to recognize, contain and resolve local sites of injury or pathogen invasion. The concept of a prototypical, “healthy” host response must, however, be modified by patient-specific (endogenous) factors, some of which will be discussed below (FIGURE 1). It can be conjectured that initial host responses are more influenced by these endogenous, host-specific factors than during later phases of SIRS where therapies/interventions, iatrogenic misadventure, and diminished host adaptability become more consequential.

Age

Over 50% of patients receiving intensive care are older than 65 years of age¹. Advancing age is clearly associated with increased morbidity and mortality. The relationship of age-related immune competence and confounding illness is, however, more complex than commonly appreciated^{54,55}. Epidemiologic data attest to the concept of “immuno-ageing” wherein pro-inflammatory, innate immune responsiveness is reasonably well preserved among many older subjects⁵⁶. The ageing population exhibits increased cytokine markers of low-grade inflammation (e.g., IL-6) and this is associated with increased risk for development of both infection⁵⁷ and other stressful events⁵⁸. Elderly subjects challenged with LPS also exhibit a more prolonged febrile response and hypotension^{56,59,60} and exhibit prolonged and enhanced cytokine responses during pneumococcal pneumonia⁶¹.

Although some theories of ageing suggest that innate immune response capacity is sustained, at least in part, by the accumulated influences of noxious challenges, such as oxidative stress⁶², there may be other interacting factors that promote pro-inflammatory competence during ageing. For instance, the diminution of autonomic variability, in particular of vagal activity, that accompanies advancing age⁴² may promote enhanced TNF α activity during initial stress. By contrast, physical conditioning enhances parasympathetic system signaling and provides a survival advantage to physically-fit elderly patients during acute inflammatory stress by attenuating cytokine excesses.

The process of immunosenescence, or age related defects in the human immune system, affect principally the adaptive immune response.^{55,56} There is a gradual loss of T cell repertoire from naïve CD8 T cells and reduced response to neoantigens in elderly subjects. Concomitantly, there is a gradual shift from a type 1 cytokine response (IL-2, IFN γ , TNF α) toward a type 2 response (IL-4, IL-6, IL-10, IL-15) that further impairs cell-mediated immunity.

Gender

It is widely assumed that gender influences the initial inflammatory response and risk profile resulting from injury. A discussion of the possible mechanisms underlying this canon is extensively presented elsewhere^{63,64}. Nevertheless, very recent single institution reports⁶⁵, multi-institutional prospective studies^{66,67}, and report compilations⁶⁸ question the validity of the assumed female gender benefit among trauma patients. There are also conflicting reports regarding gender-based responses to lesser inflammatory challenges, such to endotoxin^{69,70}. Suffice it to say that, at present, there are no consistent, gender-specific differences in systemic inflammatory responses reported among humans subjected to an initial sterile or pathogen-induced stress.

Confounding illness and treatment

There has been surprisingly little prospective correlation of acute inflammatory responses among non-cardiac surgical patients that have carefully assessed the influence of confounding illnesses. Indeed, the precise classification of relevant confounding illness remains in flux⁵⁴. Pittet et al⁷¹ noted several pre-existing conditions that influenced the outcome of bacteremia in surgical patients, including, among others, recent surgery, antibiotic therapy, and previous cardiogenic shock or resuscitation. However dated this observation may be, the importance of such conditions suggests that a recent systemic inflammatory condition may predispose to infection and adversely influence outcome.

Genetic factors

Inheritance contributes to the risk for premature, life-threatening infection⁷². Although the mechanisms for this increased risk are not defined, there are identifiable low and high inflammatory cytokine response patterns among random subjects⁷³ and a strong genetic linkage for stimulated cytokine production among monozygotic twins⁷⁴. Genome manipulations in animals clearly suggest that genetic variation within key cell signaling/response pathways may alter both local and systemic innate and adaptive immune responses⁷⁵. Genetic variation within homologous loci among humans is also likely to influence the host capacity to recognize and resolve tissue inflammation or respond to pathogen invasion. Genetic variation may also contribute to the expressed magnitude and duration of the SIRS phenotype, as suggested, for example, by variable cholinesterase activities and the resultant response to endotoxin⁷⁶.

Initial Interventions

Resuscitation—It is recognized that fluid resuscitation modifies host inflammatory responses to both infectious^{77,78} or non-infectious insults^{79–81}. Variations in fluid resuscitation regimens also result in varying inflammatory responses among older patients⁸². It is presently unknown if these initial, resuscitation modified inflammatory changes influence later immune, endocrine, and autonomic capacities during later phases of the SIRS condition. Substantial information regarding some of these issues may be forthcoming when detailed analyses of large multi-institutional studies are reported⁸³.

Antimicrobial therapy—As discussed elsewhere in this volume, there is little doubt that inappropriate use of antimicrobial therapies increases the risk of overall infection and the emergence of resistant organisms. The use of prophylactic agents in patients with initial sterile stress has received limited study as to systemic inflammatory responses. It is clear, however, that inadequate anti-microbial therapy independently increases outcome risk among SIRS patients who develop nosocomial infection⁸⁴. This adverse effect is likely enhanced among surgical patients with complex illness^{51,85}.

RESPONSES TO SUBSEQUENT INSULTS

The components of host response from an initial insult are more clearly defined than are those resulting from secondary events (FIGURE 1). The various clinical phenotypes and outcome trajectories resulting from prolonged stress in conjunction with infection have been debated for years. Several prominent overviews of this complex topic have been published^{86–89}.

While a *de novo* infectious challenge, in and of itself, yields variation in early host responses⁹⁰, the later phases of SIRS promote an even broader palette of functional system(s) phenotypes as intervention-related influences interact with endogenous determinants. There may be conflicting signals being transmitted in parallel and, in some cases, isolation of tissues from the normal, feedback controls of the uncomplicated state⁹¹. Persistent pro-inflammatory

activity is manifest, for example, by continued coagulation system activation⁹², even as other markers of pro-inflammatory activity may be waning⁹⁰. Simultaneously, variations in the competence of innate and adaptive immune defenses become evident within some tissues sites^{20,93–95}. The mechanisms underlying this evolved condition of innate immune “tolerance” and diminished capacity for neoantigens responses are more thoroughly discussed elsewhere^{21,96}. An important feature of SIRS is a persistent acute phase response that experimental studies suggest may modify both immune competence and solid organ function^{97–99}. In the context of ongoing inflammation, altered innate immune competence may occur via gene-silencing programs or other mechanisms,^{20,29,100}.

Altered rhythms during the secondary insult

Not infrequently, a prolonged stress state manifests diminishing amplitude, frequency, and efficiency of autonomic and neuro-endocrine signaling^{91,101}. By example, there have been several reports documenting diminished time domain measures of heart rate variability among critically-ill infected and injured patients^{43,102–105} that correlate to increased solid organ dysfunction and mortality risk. Reduced host adaptability, as reflected in such measures of total power, may serve as surrogate markers of organ systems “connectedness” and of overall host capacity to effectively respond to inflammatory stressors^{101,106}.

Disturbances in both short-term variability and longer-term circadian rhythmicity of neuroendocrine hormones secretion are also observed during prolonged inflammatory illness^{48,49}. Attenuated hormone rhythmicity and signal amplitude are known to associate with ischemic events⁴⁷ and may likewise contribute to disordered metabolic and immune functions^{39,48,49}. An intriguing association of reduced cardiac rate variability to adrenal cortical tolerance (or relative insufficiency) has been noted in some injured patients¹⁰⁷.

Pathogens of the second hit

The SIRS state promotes loss of adaptive immune surveillance that likely enhances virulence factor acquisition in some bacterial species^{21,50,108}. While de novo infection may elicit distinctive gene expression patterns within immune cells^{109,110}, immune cell expression signatures during acquired infections appear to converge during ongoing inflammation^{111–113}. These observations suggest that a diminished immune system repertoire (variability) reflects another aspect of altered host adaptability.

Modifiers of the secondary insult

Age—Age-related diminutions of immune and endocrine functions¹¹⁴ as well as autonomic signal attenuation may all contribute to adverse outcomes among elderly patients. There is currently limited insight across the age spectrum as to how prominently these endogenous factors contribute to loss of adaptability during prolonged stress.

Genetic factors—Most genetic association studies within seriously-ill patients have been reported from mixed populations of community-acquired and nosocomial infections. The caveats for deriving definitive conclusions from existing clinical gene association studies have been discussed^{51,53}. However, there have been some single-institution, prospective studies of highly stressed, at risk surgical populations, such as those with trauma and burns that are highly suggestive of genetic contribution to nosocomial infectious risk. For example, functional single nucleotide polymorphisms of pro-inflammatory cytokines^{51,115–117} and pathogen recognition receptors^{116,118} repeatedly associate with enhanced infection risk in stressed patients. Interestingly, these polymorphisms do not overtly modulate human responses¹¹⁹ during health but only appear to enhance risk and alter responses in the context of ongoing stress.

The influences of current treatment practices

Very little is known about how currently “acceptable” treatment practices (exogenous factors) might alter host adaptability. Several such strategies have been adopted after prospective demonstrations of improved outcomes that also exhibited some diminution of inflammatory markers. Interestingly, most of these adopted support modalities are designed to reduce signal input variance to the stressed host. Several current management practices are briefly discussed to speculate as to how invariant clinical management practices might alter the phenotypes and systemic responses of stressed patients.

Mechanical ventilation—Current management of respiratory failure conforms to protective strategies impose constraints to variations in volume, pressure, or oxygenation parameters^{120–123}. These approaches appear to promote the resolution of initial pulmonary inflammation and related organ systems dysfunction¹²³. How these management practices influence inflammatory responses to a later tissue injury or infection challenge remains a matter of some conjecture.

Glucose control—The clinical management concepts of rigid glucose level control (reduced variability) has been rapidly adopted by the intensivist community¹²⁴. There is now some reconsideration of this rigorous protocol¹²⁵ and the issue of how varying ranges of glucose and insulin control may modulate inflammatory responses remains open to question^{126,127}

Route and composition of feeding—The use of parenteral nutrition has greatly diminished as a management practice among stressed patients¹²⁸. Several inflammatory mediator responses may be potentiated during continuous parenteral feeding^{129–131}. Some data suggests that these enhanced responses may be related to the composition of parenteral feeding regimens.¹³² Importantly, either continuous enteral or parenteral feeding may dampen cellular and systemic regulatory signals exerted by autonomic and circadian rhythms¹³³. Hence, alternative management strategies designed to enhance variability of nutrient provision might further leverage any benefits of nutritional support.

SYNOPSIS

The cognate signals from either sterile or pathogen-induced sources converge on the same recognition/response pathways. In the surgical patient, a systemic response to infection most often occurs in the context of ongoing inflammatory stress. Such an inflammatory response is modulated initially by the magnitude of injury and by patient-specific (endogenous) factors, such as confounding illness, age, and genetic variation. Over an extended period of stress, treatment-related (exogenous) factors add unpredictability to host responses to subsequent challenges, such as acquired infection. The host response is discussed in the context of how existing, sterile stressors may modify the response to acquired infection in surgical patients.

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Figure 1.

The host response to an initial sterile "hit" (stress), such as trauma or surgery, includes activation of inflammation responsive systems (e.g. innate immune system) modified primarily by the magnitude of insult and patient-specific (endogenous) factors. As the systemic inflammatory response (SIRS) arising from an initial stress continues, patient management and pathogen virulence (exogenous factors) assume a more prominent influence on the balance of systems activity. Responses below the basal level generally reflect reduced end-organ responsiveness (tolerance) and reduced signal input variance (adaptability). The interactions among endogenous and exogenous factors leads to uncertainty (gray area) over time about systems activity and overall responsiveness to secondary insults, such as infection.