

Heartfelt sepsis: microvascular injury due to genomic storm

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Abstract

Sepsis is one of the ten leading causes of death in developed and developing countries. In the United States, sepsis mortality approaches that of acute myocardial infarction and exceeds deaths from stroke. Neonates and the elderly are the most vulnerable patients, with these groups suffering from the highest sepsis mortality. In both groups, many survivors respectively display serious developmental disabilities and cognitive decline. The National Institute of Health/National Heart, Lung, and Blood Institute Panel redefined sepsis as a “severe endothelial dysfunction syndrome in response to intravascular and extravascular infections causing reversible or irreversible injury to the microcirculation responsible for multiple organ failure.” Microvascular endothelial injury in sepsis due to microbial inflammation encompasses small blood vessels (< 100 μm in diameter). While the lungs remain the principal organ of interest due to sepsis-associated acute respiratory distress syndrome, “septic heart” or “septic cardiomyopathy” accelerates sepsis’ transition to potentially lethal septic shock. This review analyses both new advances in understanding the septic mechanism and possible resolutions of sepsis. The concept of a “genomic storm,” caused by microbes triggering florid production of inflammatory mediators, is based on septic reprogramming of the human genome. This genomic storm leads to microvascular endothelial injury, persistent hypotension, and organ failure. While very early control of sepsis-causing bacterial, fungal and viral infections remains crucial for the treatment of sepsis, supportive measures are likewise necessary to maintain blood pressure, respiration, and kidney function. New evidence indicates that preadmission β -blockers may reduce sepsis-associated mortality. The fundamental role of nuclear signalling in the progression and resolution of sepsis was established with a new class of cell-penetrating nuclear transport modifiers (NTMs). NTMs target the translocation of proinflammatory and metabolic transcription factors to the cell’s nucleus while also enhancing bacterial clearance in experimental polymicrobial sepsis models. The result is a 700-fold reduction in the bacterial burden of the lungs and improvement of sepsis-associated thrombocytopenia and blood markers of endothelial injury. When added to anti-microbial therapy, NTM has increased survival from 30% to 55%, when compared to antimicrobial therapy alone. Yet, the prevention of sepsis remains the most rational and beneficial path. Anti-pneumococcal vaccination has reduced the incidence of pneumonia and sepsis caused by increasingly antibiotic-resistant *Streptococcus pneumoniae* in all age groups. Similarly, the incidence of meningococcal sepsis known as “purpura fulminans” has been reduced by a recently approved vaccine thereby preventing hearing loss, neurologic damage, and limb amputations in young survivors of septic outbreaks. We urgently need further preventive, diagnostic, and therapeutic measures as the tide of sepsis rises in the United States and around the world.

Key words: endothelial injury, genome, hypotension, infection, microbial inflammation, metabolic inflammation, microcirculation, septic cardiomyopathy, septic heart, small blood vessels, β -blockers, antibiotics, immunoprophylaxis, vaccines

Kardiol Pol 2018; 76, 8: 1203–1216

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Received: 02.07.2018

Accepted: 02.07.2018

Available as AoP: 02.07.2018

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“Sometimes the heart sees what is invisible to the eye”
[H. Jackson Brown, Jr]

INTRODUCTION

The problem of sepsis, that relentless end-stage of many microbial diseases, has been close to my heart and mind for many years. I am personally motivated to find a remedy for this scourge of modern intensive care units. Therefore, I participated in the Working Group on Blood Systems Response to Sepsis convened in 2010 by the National Institute of Health/National Heart, Lung, and Blood Institute. Our group redefined sepsis as a severe endothelial dysfunction syndrome in response to intravascular and extravascular infections leading to reversible or irreversible injury to microcirculation responsible for multiple organ failure [1, 2]. The previous definition of sepsis, proposed by others in 1992, was a “systemic inflammatory response syndrome” (SIRS) [3]. This definition, popularly described as a “cytokine storm” was frequently criticised as inadequate. “Systemic inflammatory response” is the mechanism of many acute and chronic diseases caused by autoimmune, metabolic, or physical insults (e.g. trauma and burns). Usually, these conditions do not exhibit the potentially lethal hypotension characteristic of septic shock [4]. The SIRS definition of sepsis was redefined in 2016 as “a life-threatening organ dysfunction caused by dysregulated host response to infection” [5]. While improved, this definition still does not address the fundamental mechanism of organ dysfunction: the impairment or collapse of microcirculation [4]. Septic shock, a form of microcirculatory failure, is defined by the presence of tissue hypoperfusion despite normalisation of systemic and regional blood flow [6]. Persistent tissue hypoperfusion underlies the failure of multiple organs, including the heart [7].

This review focuses on the advances in understanding the mechanism of sepsis affecting several key organs. It also discusses the genomic storm’s role in sepsis development along with new experimental approaches seeking to protect small blood vessels damaged directly or indirectly by sepsis-causing microbial agents. Informative reviews focused on heart injury and dysfunction in sepsis provide an instructive analysis of heart-based changes in sepsis [7–10]. Other advances, including the potential benefit of preadmission β -blockers in reducing sepsis mortality are shedding a new light on the role of adrenergic system in sepsis [11], while the analysis of metabolic systems strives to stratify sepsis survivors from non-survivors [12, 13].

Here, we will focus on the mechanism of microvascular endothelial injury in multiple organs, including the heart, and experimental cytoprotective measures that increase survival and attenuate organ injury due to microbial and metabolic inflammation.

GROUND ZERO OF SEPSIS: MICROCIRCULATION COMPRISED OF SMALL BLOOD VESSELS

A continuous layer of endothelial cells lines precapillary arterioles, capillaries, and postcapillary venules. These endothelial

cells represent the main interface for blood-tissue exchange in heart, lung, brain, liver, kidneys and other organs. The microvascular endothelium constitutes the largest surface area of human circulation grossly exceeding that of macrovessels (arteries and veins) (Fig. 1) [14]. As illustrated in this figure, the heart and vascular system are interwoven. As a major organ, the heart is dependent on microcirculation in which capillary endothelial cell and cardiomyocyte form a cardiomyovascular unit responsible for homeostatic regulation of heart muscle. The endothelium provides anticoagulant shield, regulates blood flow, tissue perfusion and oxygenation, blood pressure, and tissue temperature. Microbial agents causing lesions in small blood vessels in an infected organ, such as the lungs in pneumonia, can rapidly compromise the endothelial function of other organs including heart (e.g. during pneumococcal sepsis). Importantly, endothelial cells in capillaries display a striking heterogeneity depending on the organ in which they are embedded [15]. The endothelium can be continuous, discontinuous, fenestrated, or sinusoidal in different organs. For example, small blood vessel endothelium is continuous in muscles and brain whereas endothelium in kidney glomeruli is fenestrated, while in the spleen sinusoids endothelium is discontinuous and porous [15]. Thus, the architecture and function of regional endothelium that comprises the cardiomyovascular unit in the heart differs from that of the neurovascular unit that comprises blood-brain barrier. From this perspective, more studies on the microcirculation in the heart (see Fig. 2, Coronary Circulation) are needed to discern its structural and functional features [16]. Moreover, organ-specific microvascular endothelial architecture demands caution in interpreting the microvideoscopic analysis of microcirculatory blood flow measured only in sublingual mucosa of patients with sepsis [17, 18].

During sepsis-causing infections that originate in different organs, the small vessel endothelial injury causes hypotension and myocardial dysfunction, microvascular leak, acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), acute brain injury, and thrombocytopenia with or without disseminated intravascular coagulation (DIC). Importantly, endothelial microvascular injury and dysfunction caused by microbial agent-induced genomic storm (see below) constitutes the common denominator for septic multi-organ failure [19–22].

PERSISTENT HYPOTENSION (VASOPLÉGIA) IN SEPSIS

Hypotension is a hallmark of sepsis. Hypotension requires vigorous resuscitation measures and rapid administration of empiric antimicrobial therapy until the infectious agent is identified [23, 24]. The vascular tone (resistance) is regulated to match blood flow to metabolic demand in order to provide adequate perfusion to tissues under different physiological conditions [15]. However, sepsis dysregulates this homeostatic mechanism. The consequent, persistent hypotension, unresponsive to adequate volume therapy, increases the risk of

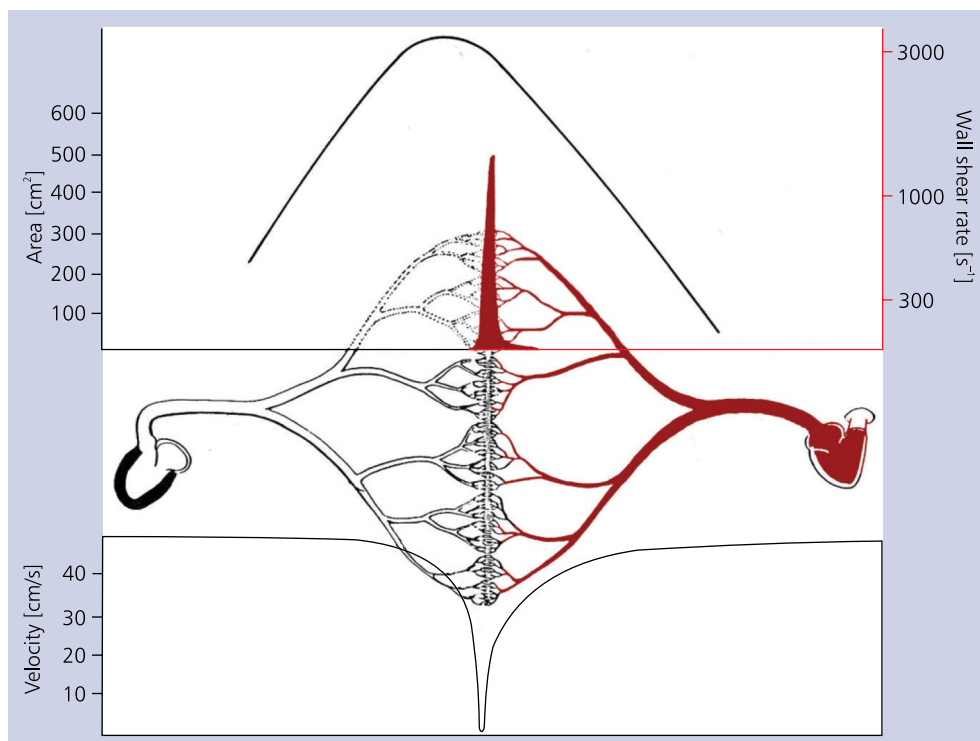


Figure 1. A global view of circulation. Arterial circulation is on the left and venous on the right. Microcirculation comprises the greatest endothelial surface area (left axis of the upper panel), as represented by the central solid peak. The upper panel right axis represents wall shear rate [s^{-1}] with the curve reaching its highest values on the arterial side of microcirculation (precapillary arterioles). The lower panel comprises the velocity of blood flow, and indicates that the slowest values correlate with postcapillary venules, the terrain of white blood cells emigration (adapted from [14])

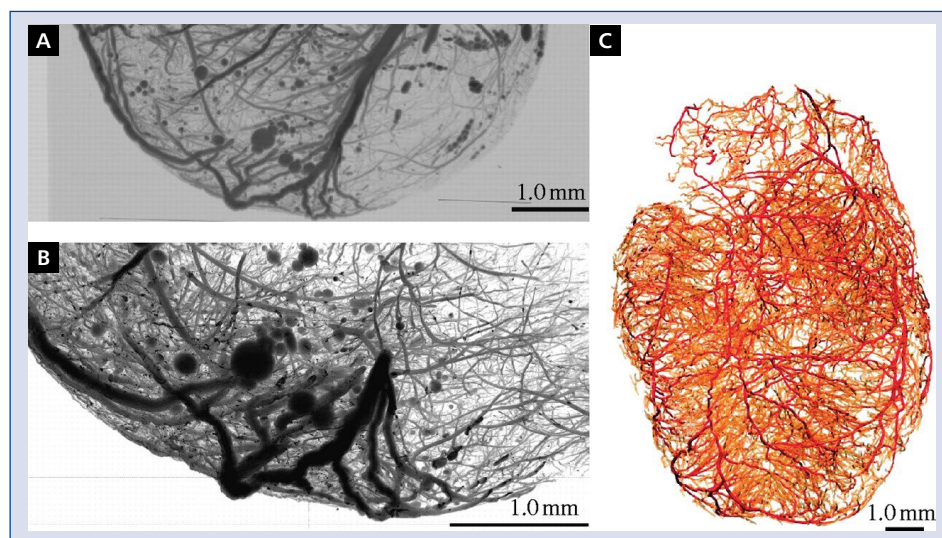


Figure 2. Micro-computed tomography imaging and segmentation of coronary vasculature. **A.** Maximum intensity projection of whole rat heart imaged at $21 \mu m$ isotropic voxel dimension; **B.** Apical portion rescanned at $4 \mu m$ (images courtesy of Prof. Erik Ritman at the Mayo Clinic); **C.** Segmented and reconstructed mesh using the automatic algorithm (adapted from [16])

lethal outcomes in sepsis [10]. Septic shock is viewed as a biphasic disorder with an early hyperdynamic phase with a high cardiac output, low systemic vascular resistance, warm extremities (“warm hypotension”) followed by a late, hypodynamic

phase with low cardiac output and poor perfusion [7]. In this setting, hypotension reflects endothelial instability and the dysregulated response to catecholamines [25]. Moreover, the increased production of nitric oxide (NO) by endothelial NO synthase (eNOS) and inducible NO synthase (iNOS), together with the generation of prostacyclin by cyclooxygenase (COX)-2, mainly contributes to hypotension in sepsis. However, NOS inhibitors were variably effective in improving sepsis-induced hypotension [26]. Alternatively, the downregulation of vasoconstrictive receptors activated by angiotensin II, catecholamines, and vasopressin may contribute to hypotension [10].

LEAKY MICROCIRCULATION IN SEPSIS

The blood-tissue barrier comprised of microvascular endothelial cells is maintained by intercellular junctions, a complex network of adhesive proteins organised into adherence junctions and tight junctions [27]. These “flood gates” to the parenchyma of different organs can be opened by a variety of microbial and host-produced factors that disrupt microvascular endothelial barrier and produce leaky small blood vessels. Microbial virulence factors include Gram-negative bacteria lipopolysaccharide (LPS), also known as endotoxin [20], staphylococcal alpha toxin [28], or Ebola virus glycoprotein [29] among others, that produce gaps in tight junctions and adherence junctions allowing the escape of blood plasma. The ensuing oedema is one of the five cardinal signs of inflammation [30]. Host-produced inducers of leaky small blood vessels include interleukin (IL)-2 [27], pleiotropic cytokine IL-6, chemokine monocyte chemoattractant protein 1 (MCP-1) [31] and vascular endothelial growth factor (VEGF), known as “vascular permeability factor” [32, 33]. They uncouple the VE-cadherin-p120 catenin complex in adherence junction. In contrast, a physiologic blood protein, Slit, stabilises intercellular junctions through binding to endothelial Robo receptor 4 [21]. Remarkably, the recombinant Slit protein increased survival in polymicrobial sepsis while cytokines remained elevated. Targeting nuclear transport of stress-responsive transcription factors (nuclear factor- κ B [NF- κ B], activator protein 1 [AP-1], nuclear factor of activated T-cells [NFAT], and signal transducer and activator of transcription 1 [STAT1]; see below) with a cell-penetrating nuclear transport modifier (NTM), cSN50 peptide, reduced leaky lung endothelial barrier disrupted by the superantigen, staphylococcal enterotoxin B [34]. Alternatively, selective targeting of transcription factor NF- κ B in endothelial cells prevented microvascular leak induced by endotoxic LPS or associated with experimental polymicrobial sepsis. These countermeasures illustrate the importance of cytoprotection of failing microcirculation in an experimental sepsis control [20, 21].

BIOMARKERS OF ENDOTHELIAL INJURY IN SEPSIS

Biomarkers produced by sepsis-activated and injured endothelium during sepsis can inform about its dysfunction [35].

Among them, endothelial cell-produced cell adhesion molecules comprise E- and P-selectins. E-selectin is expressed due to genomic upregulation evoked by LPS, the primary virulence factor of Gram-negative bacteria, and by cytokines, such as tumour necrosis factor- α (TNF- α). E-selectin is then released into the bloodstream [36, 37]. P-selectin is expressed by activated platelets and endothelial cells. P-selectin mediates platelet — leukocyte and platelet — endothelial cell interactions while contributing to thrombi formation [38]. Selectins can be measured in plasma (rather than in serum to protect them from proteolysis during blood clotting and retention in the blood clot) of patients with sepsis and in experimental animals [39].

THROMBOCYTOPENIA AND DISSEMINATED INTRAVASCULAR COAGULATION IN SEPSIS

Circulating blood platelets are surveyors of endothelial integrity [40]. They respond to any break in the continuity of endothelial layer. A decrease in platelet count below $150,000/\mu\text{L}$ has long been recognised as a hallmark of Gram-negative bacteremia and ensuing sepsis [41]. Thrombocytopenia in sepsis is due to trapping of circulating platelets in zones of endothelial injury [42]. Platelets are also susceptible to cytolytic microbial toxins or the membrane attack complex of complement activated by microbial agents [43]. Heparin is known for inducing of anti-platelet factor 4 antibodies, a hallmark of heparin-induced thrombocytopenia. Moreover, anti-microbial therapy may elicit drug-induced thrombocytopenia [44]. In a retrospective study of 304 patients (mean age 68.8 ± 15.8) with severe sepsis or septic shock, 47.6% developed thrombocytopenia, which was drug-induced in 17.9% of patients [44]. Significantly, thrombocytopenic patients suffered more episodes of bleeding and were more prone to AKI and ARDS, thereby implying protective role of platelets in repairing breaks in the microvascular endothelium. These patients had elevated serum lactic acid and prolonged requirement for vasopressors suggesting more severe microvascular endothelial dysfunction.

Thrombocytopenia in sepsis may be associated with DIC. This form of microvascular thrombosis evolves in reaction to a rapid and widespread microbial injury to microvascular endothelium. DIC was observed in 37% of a subset of 145 patients with thrombocytopenia as a complication of severe sepsis and septic shock diagnosed in a larger cohort of 304 patients [44]. The importance of prolonged prothrombin time and thrombocytopenia in predicting disease severity and survival was stressed in a study of 40 patients with severe sepsis or septic shock who were scored for DIC using the International Society on Thrombosis and Haemostasis diagnostic criteria; 95% had fibrin-related markers (fibrin monomer and D-dimer) [45].

Injury to endothelium directly activates the coagulation cascade through assembly of a prothrombinase complex linked to phosphatidyl serine exposed on injured endothelial cell membrane [46]. This mechanism of thrombin formation in microcirculation seems to bypass the need for tissue factor

pathway that was unsuccessfully targeted in clinical sepsis trials [26].

Thrombin generated on the surface of injured endothelium is required for activation of physiologic anticoagulant mechanism represented by the thrombomodulin-protein C axis [47]. Unexpectedly, a supra-normal dose of protein C zymogen concentrate had no significant effect on LPS-induced biomarkers of coagulation, fibrinolysis, and inflammation while significant protein C activation and production of TNF- α were detected in human volunteers [48].

There is a continuing uncertainty about heparin therapy in DIC. A well-designed prospective study is needed, especially with different molecular forms of heparin. Early IV administration of unfractionated heparin was associated with a 12% relative risk reduction in mortality in a retrospective propensity-matched cohort study [49]. Similarly, clinical trials of antithrombin and thrombomodulin were ineffective [26].

Thrombin interacts with PAR1 expressed on microvascular endothelial cells triggering the signalling pathway to the nucleus that culminates in nuclear transport of stress-responsive transcription factors (SRTFs), NF- κ B and AP-1, and a loss of barrier function [50]. These SRTFs mediate the production of barrier-disrupting cytokine IL-6 and chemokine MCP-1 [31, 51].

MICROVASCULAR INJURY IN THE HEART DURING SEPSIS: “SEPTIC HEART” AND “SEPTIC CARDIOMYOPATHY”

Septic cardiomyopathy has been known for at least 40 years, being recognised in 44% patients with sepsis whose likelihood of the fatal outcome is raised two to three times [7].

The autopsy study of the hearts in sepsis non-survivors, with a mean age of 59 years and who spent on average 24 days in the intensive care units, revealed loss of distinct cross-striations and lysis of myofilaments in longitudinal sections of myocardium. Lipofuscin granules indicated oxidative stress. Significant mononuclear cell infiltrates (macrophages?) in the interstitium were prominently displayed including the expression of TNF- α , which was also detected in cardiomyocytes, vascular smooth muscles, and endothelial cells as compared to control hearts (obtained from accident victims without chest injury) [9]. Some of these features of the septic heart were replicated in experimental polymicrobial sepsis model based on cecal ligation and puncture. In this model, dystrophin-glycoprotein complex was disrupted thereby impairing contractile force transmission, a sign of the mechanical dysfunction during cardiomyopathies. The loss of this complex reduces the mechanical integrity of the cardiac muscle rendering it more susceptible to inflammatory insults [9]. As individual cardiomyocytes are connected by cell-cell junctions located in intercalated discs, these intercellular communication channels are also altered in experimental model of polymicrobial sepsis. This contributed to the reduc-

tion of mean ejection fraction, fractional shortening, cardiac output, and heart rate. Such abnormalities are also linked to intracellular calcium overload counteracted in part by the calcium blockers, dandrolene or verapamil [9, 52, 53]. In another experimental model of polymicrobial sepsis with fluid resuscitation, 527 gene transcripts representing inflammatory and cell cycle pathways were significantly upregulated or downregulated in septic heart. This genomic reprogramming was accompanied by mitochondrial swelling and myocardial depression [54].

In the realm of clinical sepsis, magnetic resonance studies of the heart suggested reversible myocardial oedema or an altered metabolic state, clearly distinct from ischaemia and necrosis. Also, a reversible Takotsubo cardiomyopathy (broken heart syndrome) pattern has been reported in patients with sepsis. Finally, Ehrman et al. [7] concluded that echocardiographic measures of left (systolic or diastolic) and right ventricular function cannot provide reliable prognostic information in patients with sepsis. Similarly, they questioned the utility of natriuretic peptide and troponin measurements.

MICROVASCULAR ENDOTHELIUM IS UNDER THE SIEGE BY SEPSIS-CAUSING MICROBIAL AGENTS RANGING FROM GRAM-NEGATIVE BACTERIA TO EBOLA VIRUS

Gram-negative bacteria produce LPS, known as “endotoxin,” that is a very potent proinflammatory virulence factor inducing genomic storm in humans and experimental animals (see below) [51]. *Rickettsiae*, which cause epidemic typhus and Rocky Mountain spotted fever (RMSF), demonstrate astonishingly effective entry and spread within microvascular endothelium to produce signs of rapidly evolving septic shock. The RMSF microbial agent, *Rickettsia rickettsii*, transmitted by an infected tick, is a frequent offender in the southeastern United States. It causes fever, headaches, myalgias and petechial rash in 85% of patients [55]. Relevant to the scope of this review, it may cause myocarditis manifested by chest pain, elevated cardiac enzyme levels, and myocardial dysfunction mimicking coronary heart disease [56]. A prospective study of vaccinated and unvaccinated volunteers infected with *Rickettsia rickettsii* and promptly treated with antimicrobial therapy has demonstrated laboratory evidence of microvascular endothelial activation and injury [57].

More dramatic microvascular endothelial injury with florid bleeding diathesis is noted in patients infected with Ebola virus during recent epidemic outbreaks in Africa [58]. Rapidly spreading Ebola virus employs a virion glycoprotein that preferentially binds to endothelial cells, causing their death within 12 to 16 h [29]. Once inside the endothelial cells, the virus deploys VP24 protein to disarm the host innate immune response mediated by interferons. Moreover, it undermines anti-viral antibody production by expressing

a defensive decoy made of truncated virion glycoprotein [59, 60]. Of note, a patient's genomic signature encoding HLA proteins determines whether the infected patient survives or dies from sepsis caused by the Sudan species of Ebola virus [61]. HLA represents the most polymorphic region in human genome that includes the human leukocyte antigen-B locus. Thus, alleles B*67 and B*15 were associated with fatal outcome whereas B*07 and B*14 hailed survival, indicating that these alleles control host response to Ebola virus and the outcome of sepsis. These lessons from Ebola virus sepsis call for a similar genomic analysis of human sepsis due to other microbial agents to predict more precisely its course and outcome.

GRAM-NEGATIVE BACTERIA DOMINATE THE SEPSIS BATTLEFIELD

Two-thirds of patients with sepsis are infected with Gram-negative bacteria either alone or together with other microbial agents [62]. Sepsis-causing bacteria rapidly propagate before effective, pathogen-directed anti-microbial therapy is initiated. They reach a quorum (stationary phase) during which their genes encoding virulence factors are activated and their products released [63]. LPS (also known as endotoxin), an integral component of the outer membrane of Gram-negative bacteria, is highly diverse. Different strains of Gram-negative bacteria display structurally-distinct LPS including its toxic component lipid A [64]. Hence, the biologic activity of LPS differs, as exemplified by *Escherichia coli* and *Neisseria meningitidis* [65]. Analysis of systemic inflammation induced by LPS derived from a single bacterial species provides valuable information about the mechanism of action of that particular LPS. However, a polymicrobial sepsis model, which is based on intraperitoneal injection of gut microbiome ("cecal slurry"), infects the host with a multitude of Gram-negative bacteria expressing diverse LPS structures and additional virulence factors as well as Gram-positive bacteria and other microbes [39, 66]. In this clinically-relevant model, the host's defenses are multiply challenged by diverse bacteria thereby raising the bar for testing new and more effective countermeasures.

Sepsis-causing microbial agents are aided by the host-produced inflammatory mediators in damaging microvascular endothelium [4]. These "co-conspirators" include complement factors, cytokines, chemokines, adhesion molecules, inducible COX-2 and NOS metabolites. In addition, damaged cells release their constituents' termed host endogenous products, e.g. haemoglobin [67, 68] that add insult to initial injury exerted upon microvascular endothelial cells. Hence "anoikis," apoptosis of endothelial cells detached from extracellular matrix, ensues. These detached and "homeless" endothelial cells circulate in blood and can be detected, counted and characterised, including increasingly available genomic analysis [69].

SPEEDY IDENTIFICATION AND TREATMENT OF SEPSIS-CAUSING MICROBES TO AVERT A FULL BLOWN GENOMIC STORM

Traditional and lengthy methods of microbiologic diagnosis based on culture and identification of suspected microbial agents are being gradually replaced by novel methods of microbial detection. In addition to the real-time polymerase chain reaction-based techniques, new methods of fluorescent in situ hybridisation, matrix-assisted laser desorption/ionisation-time-of-flight mass spectrometry are speeding up turnaround time to about 30 to 150 min for staphylococci and their anti-bacterial resistance elements [70]. These diagnostic advances allow early administration of the specific pathogen-directed anti-microbial therapy during the first "golden hour," including patient's prehospital settings. Of course, the ultimate goal is to gain an early hold on invading microbial agent to avert wide-spread microvascular changes in patients suspected of harbouring sepsis-causing infections. While bacteria are being eliminated, their virulence factors (e.g. LPS, staphylococcal and streptococcal toxins, anthrax toxins) may not desist after initiation of pathogen-directed anti-microbial therapy. These virulence factors can remain in microcirculation and continue to inflict damage to blood cells and microvascular endothelial cells unless the host's innate and adaptive immune systems execute a rapid clearance of microbial agents and their toxic virulence factors [41, 71].

GENOMIC STORM IS CAUSED BY MICROBIAL VIRULENCE FACTORS THAT RAPIDLY REPROGRAMME HUMAN GENOME

When their growth remains unrestrained, especially in extravascular loci less readily penetrated by anti-microbial agents, bacteria reprogram their genomes through a quorum sensing mechanism and produce multiple virulence factors that potentiate microvascular injury [63, 72, 73]. As depicted in Figure 3, bacterial and fungal virulence factors and viral nucleic acids initiate the host's innate immune response. Its mainstays are the pattern recognition receptors, e.g. toll-like receptors (TLRs), present in immune cells and non-immune endothelial and epithelial cells [74, 75]. TLR4 is a canonical receptor for LPS, a virulence factor known as the most active biologic inducer of systemic inflammation [76].

Toll-like receptors initiate signalling cascades to the nucleus upon binding of microbial virulence factors and other products. These cascades activate SRTFs, such as NF- κ B, AP-1, NFAT, and STAT-1 α (Fig. 3) [77]. Each of them, either alone or in combination, activates multiple genes that encode pro-inflammatory cytokines and chemokines, as well as their receptors, signal transducers, and cell adhesion molecules. This "across the board" activation of hundreds of genes in humans and experimental animals is termed a genomic storm [51, 78].

The products of multiple genes activated during genomic storm mediate fever, microvascular endothelial instability

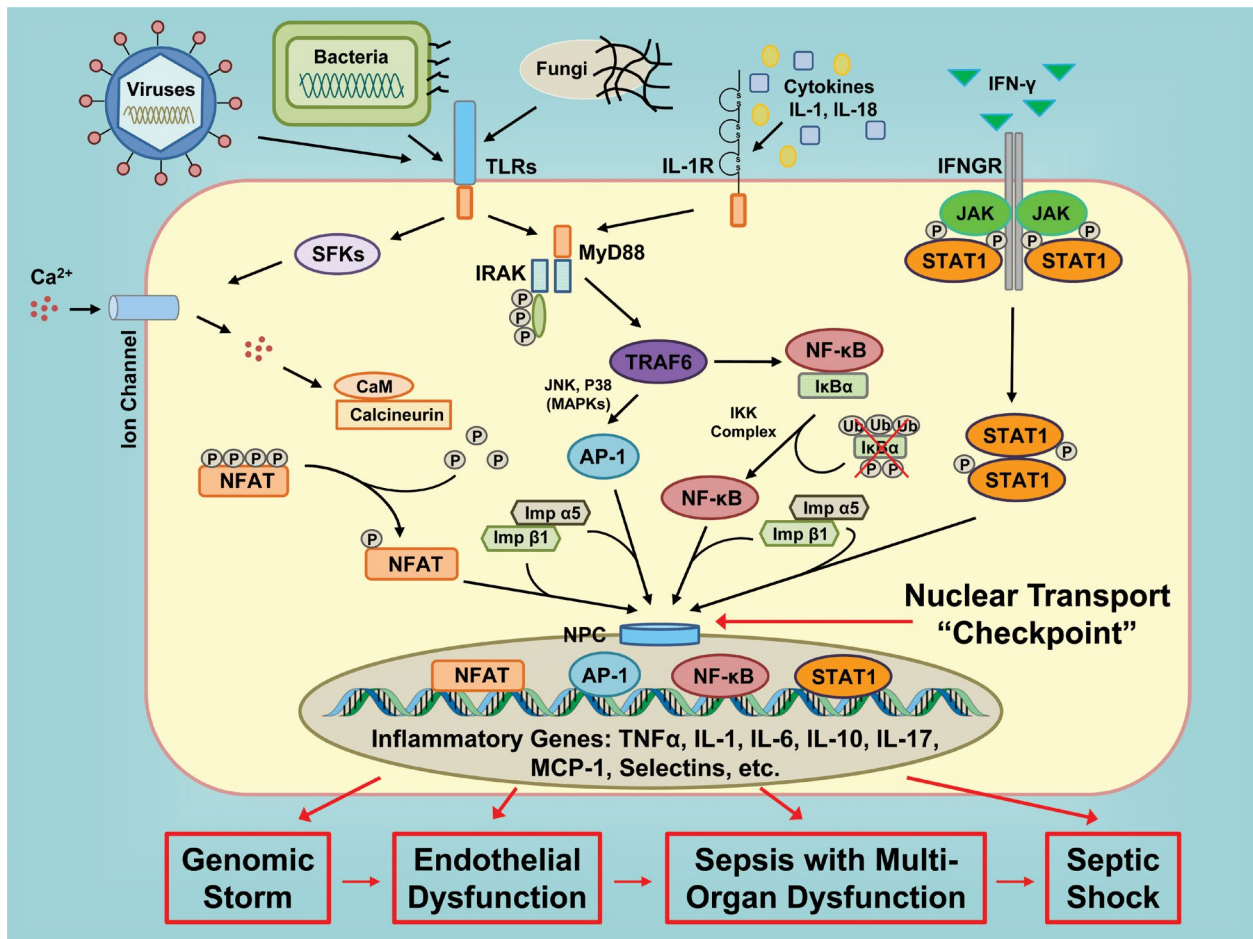


Figure 3. Nuclear transport is a pivotal checkpoint in genomic regulation of microbial inflammation. Inflammatory signalling cascades initiated by cell responses to microbial virulence factors and cytokines culminate in nuclear translocation of stress-responsive transcription factors (SRTFs) that upregulate inflammatory gene networks. Unchecked, this genomic reprogramming (genomic storm) leads to endothelial dysfunction, multi-organ failure, and ultimately fatal shock. Inhibiting nuclear transport at a common “checkpoint” located downstream of toll-like receptors (TLRs) and cytokine receptors globally suppresses expression of inflammatory genes thereby calming the genomic storm and averting multiple organ injury; AP-1 — activator protein 1; Ca^{2+} — calcium ions; CaM — calmodulin; IFNGR — interferon-gamma receptor; $\text{IFN-}\gamma$ — interferon-gamma; IKK — I kappa B kinase; IL-1, IL-6, IL-10, and IL-17 — interleukin 1, 6, 10 and 17, respectively; IL-1R — interleukin 1 receptor; Imp α 5 — importin alpha 5; Imp β 1 — importin beta 1; IRAK — interleukin-1 receptor-associated kinase; $\text{I}\kappa\text{B}\alpha$ — NF- κ B inhibitor alpha; JAK — Janus kinase; JNK — c-Jun N-terminal kinase; MAPKS — mitogen-activated protein kinases; MCP-1 — monocyte chemoattractant protein-1; MyD88 — myeloid differentiation primary response 88; NFAT — nuclear factor of activated T cells; NF- κ B — nuclear factor kappa B; NPC — nuclear pore complex; P — phosphate group; SFKs — Src family of protein tyrosine kinases; STAT1 — signal transducer and activator of transcription 1; $\text{TNF}\alpha$ — tumour necrosis factor alpha; TRAF6 — TNF receptor-associated factor 6; Ub — ubiquitin (adapted from [39])

responsible for low blood pressure, microvascular endothelial injury that underlies acute respiratory distress syndrome, disseminated intravascular coagulation, and multiple organ dysfunction, culminating in potentially lethal vascular collapse refractory to vasopressors and fluid resuscitation, a condition known as septic shock [2, 79]. Thus, signalling to the host cell’s nucleus constitutes a fundamental process of microbial inflammation evolving from innate immunity [77].

GENOMIC STORM IN EXPERIMENTAL POLYMICROBIAL SEPSIS CAN BE EXTINGUISHED BY TARGETING NUCLEAR TRANSPORT OF SRTF

Sepsis non-survivors displayed strikingly increased levels of a key SRTF, NF- κ B, in nuclei of peripheral blood mononuclear cells [80]. In agreement with this hallmark of human sepsis, we found not only increased nuclear content of NF- κ B1 (p50) and NF- κ B RelA (p65) but also phosphorylated STAT-1 α (MW91),

phosphorylated STAT1 α (MW84) and AP-1 (cFos) in liver cells of septic animals comprising hepatocytes, macrophages, and microvascular endothelial cells, among other cells [39].

This multi-stage process of proinflammatory and metabolic signalling to the cell's nucleus can be interrupted by targeting nuclear transport, a pivotal checkpoint integrating translocation of multiple transcription factors to the nucleus (Fig. 3). Thus, instead of targeting one signalling cascade of individual transcription factor, it would be a more efficient strategy to inhibit in a one swipe several signalling cascades that converge at the nuclear import step. This concept was proven by design and development of NTMs [4, 51, 77, 81].

Nuclear transport modifiers have been shown to inhibit nuclear translocation of SRTFs, such as NF- κ B, AP-1, NFAT, and STAT-1 [82], and sterol regulatory element binding proteins (SREBPs) [81] thereby impeding nuclear delivery of proinflammatory and metabolic transcription factors. NTMs displace nuclear import cargo from its binding pocket on importin α 5 and importin β 1, that translocate SRTFs and metabolic transcription factors SREBPs to the nucleus. Thereby, signal transduction pathways, which culminate in genomic reprogramming, can be controlled [51, 81]. Importin β 1 is a sole transporter of SREBPs to the nucleus [81]. NTM's signal sequence hydrophobic region (SSHR) that inhibits binding of SREBPs to importin β 1 also serves as a membrane translocating motif to enable intracellular delivery of peptides and proteins through an ATP- and endocytosis-independent mechanism [83]. Consequently, proinflammatory reprogramming of the genome is prevented in multiple cells that slow down producing inflammatory, procoagulant, proapoptotic, and autoimmune mediators. Hence, inflammatory responses, microvascular injury, apoptosis and haemorrhagic necrosis are suppressed with a concomitant gain in survival, in models of lethal shock induced by bacterial toxins [34, 84–86]. Strikingly, NTM reduced plasma levels of 23 out of 26 LPS-induced proinflammatory cytokines, chemokines, and growth factors thereby calming the genomic storm [51]. Some of these NTM-suppressed cytokines (TNF- α , IL-1, IL-6, and IL-17) are targeted solo by expensive monoclonal antibody therapy.

In an experimental model of polymicrobial sepsis, simultaneous targeting of nuclear transport adaptors importin α 5 and importin β 1 with NTM not only attenuated nuclear import of SRTFs and maintained metabolically-important glycogen stores in the liver but significantly reduced bacterial burden in blood, spleen, and lungs. The clearance of bacteria in the lung was increased 700-fold prior to the initiation of anti-microbial therapy (Fig. 4). Moreover, NTM attenuated proinflammatory cytokines and chemokines in blood, preserved normal platelet count in blood, and reduced plasma markers of microvascular injury (Fig. 4) as well as neutrophil infiltration of the liver [39]. These apparent cytoprotective effects of NTM contributed to a significant gain in survival from 30% on antibiotic therapy alone to 55% on combination of NTM with antibiotic (Fig. 5).

METABOLIC DERANGEMENTS IN SEPSIS

The impact of sepsis on human body metabolism has been analysed in a large cohort of patients with suspected, community-acquired sepsis [12]. The great majority of patients with sepsis caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Escherichia coli* survived, with a 28-day mortality of 4.9%. Non-survivors and survivors consistently showed divergent values in several metabolic parameters studied. First, as predicted, lactate, an established marker of sepsis severity, was elevated in sepsis non-survivors group. Second, alterations in fatty acid metabolism produced a prominently different metabolomic phenotype of sepsis survival and death. Six plasma carnitine esters were decreased in sepsis survivors. In contrast, 16 carnitine esters and four fatty acids were elevated in sepsis non-survivors as compared to controls. In agreement with a previous study [87], this analysis points to a consistent defect in β -fatty acid oxidation in sepsis non-survivors attributed to a malfunctioning mitochondrial shuttle for acyl carnitines. Their excess in plasma may cause ventricular diastolic dysfunction of the heart [88]. The plasma proteome analysis established that 22 complement components were elevated in sepsis non-survivors along with nine fatty acid transport proteins. As fatty acid metabolism, along with that of triglycerides and cholesterol, is transcriptionally regulated by SREBPs, their role in sepsis-induced metabolic dysregulation awaits further studies (see above).

Recently, McGarrity et al. [13] reported metabolic system analysis of LPS-induced endothelial dysfunction and its potential application to the stratification of patients with sepsis. They built Genome Scale Metabolic Model (GEM) for resting and activated human endothelium and found that patient plasma from non-survivors displays increased glycan metabolism.

SEPSIS AT THE EXTREMES OF AGE

Among all age groups, infants and elderly are most susceptible to sepsis and its fatal outcome. Among infants, neonatal sepsis survivors are prone to development of life-long disabilities. As the newborn immune system is immature, including dysregulated physiologic anti-inflammatory suppressors [89], the susceptibility to uncontrolled activation of inflammatory cascades is heightened. Uninfected prematurely born infants, who display the highest levels of IL-18 exceeding those in healthy adults, are particularly susceptible to sepsis [90]. IL-18 in adults is associated with hypotension, acute lung injury, and lethal shock. We established a novel axis that comprises IL-18/IL-1R1/IL-17A and underlies neonatal sepsis. Accordingly, genetic or pharmacologic targeting of IL-17 signalling pathway prevented the enhancement of experimental neonatal sepsis mortality in a relevant experimental model [90]. As monoclonal antibody targeting IL-17 is available, this new advance in neonatal sepsis opens up a potential method of treatment.

At the other end of the age spectrum, incidence and mortality due to sepsis are the highest among patients above

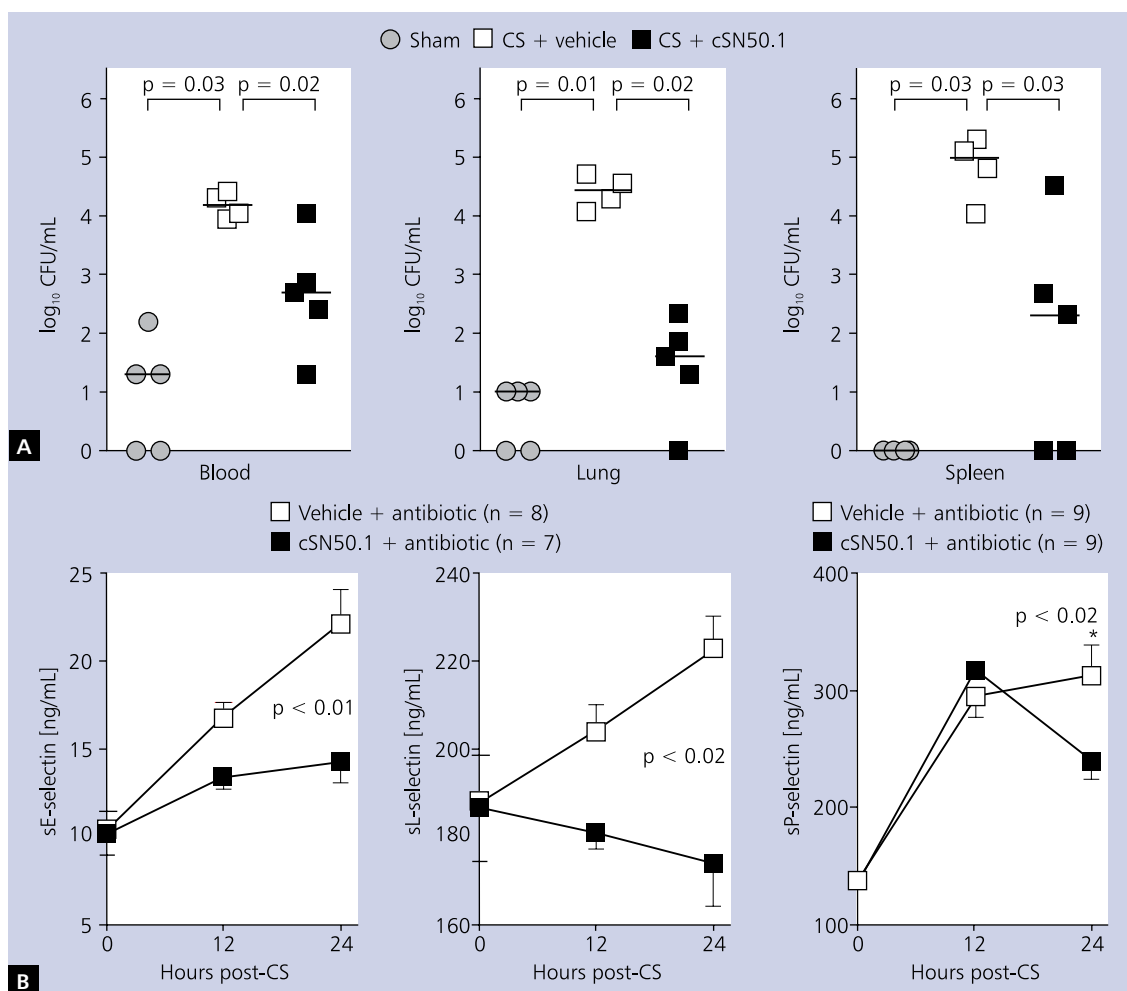


Figure 4. Improvement of bacterial clearance and biomarkers of endothelial injury in infected mice treated with nuclear transport modifier (NTM) (cSN50.1 peptide). **A.** Colony-forming units (CFU) determined by serial dilution of whole blood and organ homogenates collected 12 h after infection from sham- or gut microbiome-containing cecal slurry (CS)-infected mice treated with NTM (cSN50.1 peptide) or vehicle. Bars represent median values from four to five mice/group (*p* values determined by Mann-Whitney test); **B.** Endothelial and leucocyte biomarkers, namely, soluble E-selectin, L-selectin, and P-selectin measured in blood plasma before and at 12 h and 24 h after CS infection. Antibiotic therapy with meropenem began at 12 h post-infection (*p* values for sE-selectin and sL-selectin calculated by two-way repeated measures ANOVA, *p* value for sP-selectin determined by Mann-Whitney test at 24 h only, *n* = 9/group) (adapted from [39]); **p* < 0.05 only at 24 h. The vertical line represents the standard error of the mean (SEM), and squares represent the mean values

65 years of age [79]. Advanced age-related immune decline is likely to combine with physiologic ageing in which defective nuclear lamin processing is associated with nucleoplasmic lamin A/C and vascular ageing in the normal population [91]. Increased susceptibility to sepsis is also observed in accelerated ageing (Hutchison-Gilford progeria) [92]. Accelerated ageing is caused by mutations in nuclear lamins. Laminopathies are linked to transcriptional dysregulation, oxidative stress, inflammatory signalling, vascular smooth muscle apoptosis, and accelerated atherosclerosis [93]. We found that innate immunity adaptor SARM protects lamins from inflammation-induced apoptotic degradation [94].

Moderate-to-severe cognitive impairment was discovered in a large cohort of sepsis survivors as compared to non-sepsis

patients [95]. Sepsis survivors encompass not only elderly patients who suffer from rapidly progressing cognitive decline. More recent prospective study of employment among the younger survivors of critical illness (cardiogenic or septic shock) revealed that approximately half was unemployed after their illness [96]. Moreover, impaired cognitive function at 12 months after hospital discharge was a predictor of subsequent employment status.

These troubling outcomes of sepsis and other critical illnesses have profound consequences for patients, their families, and societal resources for long-term care. Hence, they add immeasurably to the high human and economic cost of sepsis that exceeded \$20 billion in the United States in 2011 [97].

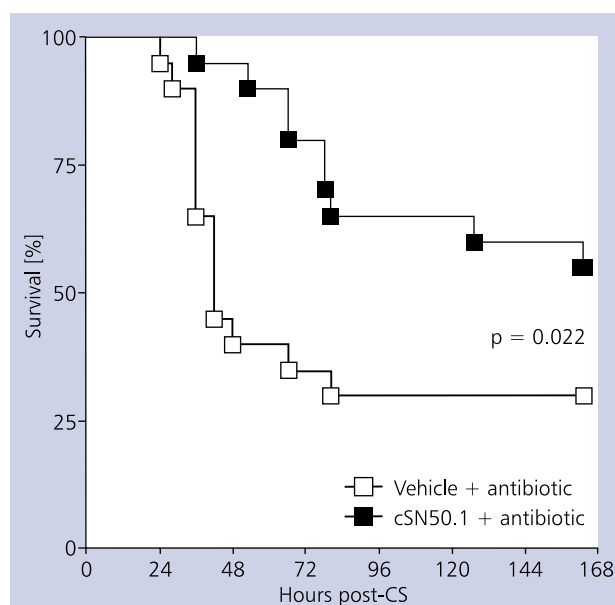


Figure 5. Survival is increased by combining nuclear transport modifier (NTM) (cSN50.1 peptide) treatment with antibiotic therapy. Mice were infected with gut microbiome termed “cecal slurry” (CS) and treated with vehicle or NTM (cSN50.1 peptide), both supplemented by antibiotic therapy with meropenem ($n = 20$ mice/group; Kaplan-Meier survival plot with p value calculated by log-rank analysis) (adapted from [39])

IMMUNOPROPHYLAXIS OF SEPSIS

Vaccines against microbial agents that cause sepsis significantly impact the incidence of sepsis-causing infections. The incidence of pneumococcal sepsis due to infection with *Streptococcus pneumoniae* has been greatly reduced. The potentially fatal complications in patients with pneumonia, and those born with asplenia, sickle cell anaemia, and undergoing splenectomy are prevented. Strikingly, administration of pneumococcal vaccine to children reduced dramatically childhood pneumococcal sepsis but also adult sepsis [98]. Remarkably, non-vaccinated older adults, including the 65–74- and 75–84-year-old age groups, displayed a significant reduction in hospitalisation for pneumonia and its invasive complication, sepsis. This important example of “herd immunity” teaches us that consistent vaccination of children, as the main carriers of targeted microbial agent (*Streptococcus pneumoniae*), reduces its transmission to parents, grandparents, and other adults in contact with children. Presently this vaccination has been extended to older age groups as well.

Likewise, a vaccine against group B *Neisseria meningitidis* reduced the incidence of meningococcal sepsis among college students and military recruits. Rarely, a patient with purpura fulminans is now being encountered in paediatric and adult emergency rooms. Patients with deficiency of blood complement membrane attack complex are particularly prone to

meningococcal or gonococcal sepsis. While antibiotic therapy is effective in limiting rapidly progressing microvascular injury, young patients with meningococcal sepsis suffer not only from hearing loss and neurological damage but also lose their limbs due to amputations [99]. Similarly, patients with the inborn defects of innate immunity (IRAK-4 and MyD88 deficiencies detected through genomic diagnosis of children with recurrent infections) should be immunised with *S. pneumoniae* conjugated and nonconjugated vaccines, *Haemophilus influenzae* conjugated vaccine, and *Neisseria meningitidis* conjugated and nonconjugated vaccines [100]. Clearly, immunoprophylaxis is the most rational and beneficial method of sepsis prevention.

FUTURE OUTLOOK

While working among colleagues who take care of patients with sepsis, I share their frustration with a continuing lack of new cytoprotective drugs approved for treatment of sepsis and its sequelae. Likewise, there is a woefully slow pace of development of new antimicrobials. Advances in immunoprophylaxis such as Ebola virus vaccine are also slow to come. The heart-wrenching consequences of sepsis in neonates who survive and suffer from developmental disabilities and in the middle-aged or elderly survivors, who experience a cognitive decline adversely affecting their prospect for employment and independent living, evoke a call to action.

All of us benefit directly or indirectly (“a herd immunity”) from the pneumococcal vaccine. Younger individuals are also protected by meningococcal vaccine when they enter college or military service. Hence, they (and their parents) no longer fear purpura fulminans. However, immunoprophylaxis for other sepsis-causing Gram-negative bacteria and staphylococci is lagging behind. It is partly due to a huge diversity of Gram-negative bacteria and the pervasive make-up of staphylococci. Luckily, steady progress with anti-microbial monoclonal antibodies bodes well for this form of immunoprophylaxis or immunotherapy. Ideally, ultra-rapid identification of sepsis-causing microbial agents should be met with the development of a panel of therapeutic cross-reactive monoclonal antibodies crafted for a group of related pathogens. A patient’s genome susceptibility loci identified by whole genome sequencing should be available with proper privacy guidelines from his/her electronic health record to map the optimal preventive and therapeutic strategies. In parallel, comprehensive countermeasures for sepsis-mediating genomic storm are emerging as therapeutic companion to antimicrobials and anti-microbial monoclonal antibodies.

Getting there in a heartbeat should be “a dream with the deadline” for all involved.

Acknowledgements

This article is dedicated to the memory of Zdzisław Przybyłkiewicz, Zygmunt Hanicki, Jan Bóbr, Andrzej Szczeklik,

Janusz Jeljaszewicz, Edward Kowalski, and Stefan Niewiarowski whose guidance and friendship during my formative years in Collegium Medicum of the Jagiellonian University in Kraków and at the National Institute of Hygiene in Warsaw helped me become a physician-scientist in continuing search for new answers to the old problems in biomedicine.

I thank Józef Zienkiewicz and Adam Hawiger for their help in preparation of this article. I also thank Ruth Ann Veach, Yan Liu, Daniel Robinson, Danya Liu, Chunsheng Li, Yiliu Chen, Sheila Downs, Jadwiga Grabarek, Vernon Reinhold, Amy Major, Martha Hutchens, Antonio DiGiandomenico, Yao-Zhong Lin, Daniel Moore, Huan Qiao, Chad Sethman, Troy Torgerson, Jim Wynn, Łukasz Wyleziński, and Józef Zienkiewicz for their contributions to the ongoing and past projects conducted in my Laboratory and cited in this article.

The author's experimental work cited in this article was supported during the past three decades by the National Institutes of Health grants R01HL085833, R01AA15752, R01HL087531, R01HL069452, T32HL069765 (J.H.), K08DK090146, F32HL099140, F32HL084214, and F32HL087531. Currently, VA MERIT grant 11O1 BX002750 is supporting our research on microbial and metabolic inflammation. Also, funds for Endowed McGavock Chair are provided by Vanderbilt University. Core services are funded in part by scholarships from the Vanderbilt University Medical Centre Digestive Disease Research Centre, supported by NIH grant P30DK058404, the Vanderbilt Diabetes Research and Training Centre supported by NIH U24DK59637, and the Vanderbilt Ingram Cancer Centre, supported by NIH grant P30CA68485. Additional support was provided by the Department of Medicine at Vanderbilt University, the Vanderbilt University Medical Centre Immunotherapy Program, and the Vanderbilt Clinical and Translational Science Award UL1TR000445. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The author apologises to those whose work was omitted from the reference list because of a limit on the number of cited references.

Conflict of interest: Jacek Hawiger is a co-inventor of multiple patents issued and pending relating to cell-penetrating NTM peptides and their use for anti-inflammatory therapy. All rights are assigned to Vanderbilt University.

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Cite this article as: Hawiger J. Heartfelt sepsis: microvascular injury due to genomic storm. *Kardiol Pol*. 2018; 76(8): 1203–1216, doi: [10.5603/KP.a2018.0146](https://doi.org/10.5603/KP.a2018.0146).