

Disseminated Intravascular Coagulation – The Hemorrhagic Hurricane and the Cytokine Storm

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*Wind and clouds,
Expanding storm,
Explode-Implode
In time.
Then silence forms;
Thoughts emerge.
Strength grows
and
Life reforms.
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Sepsis is defined as the dissemination of infection throughout the vascular tree and circulating blood. All pathogens from bacteria to viruses, fungi and parasites produce sepsis. Severe septic states have a high associated mortality, up to 25% in bacterial sepsis, and even higher, up to 40-70% with viremia. The worst infections where there is shock produce a 'cytokine storm' with an excess outpouring of inflammatory cytokines and inflammatory cell activation and invasion. This cytokine storm is followed by a loss or attrition of normal immune responses. Once triggered, this cytokine storm can initiate coagulation with microvascular clotting causing occlusion of small vessels which in turn cause ischemia of multiple organs, resulting in circulatory collapse, pulmonary distress and renal failure. This widespread vascular clotting can then deplete clotting factors generating subsequent bleeding, a condition called disseminated intravascular coagulation (DIC). With DIC the mortality in septic shock is even higher, as noted, up to 40% to 70% in viral sepsis. We are proposing that this clotting and bleeding disorder (DIC) be called the 'Hemorrhagic Hurricane', as the bleeding partner to the 'Cytokine Storm'. Produced by aberrant responses in the arterial vessels and circulating blood, these inflammatory and coagulation disorders in septic shock are, in effect a form of vascular disease. Both the 'cytokine storm' and the 'hemorrhagic hurricane' in severe septic states remain an unmet therapeutic need in vascular and hematological diseases and mortality in septic shock remains high.

In a septic shock state there is a loss of vascular competence (leaky capillaries), causing hypotension and end-organ ischemia due to reduced blood flow with limited oxygen, and/ or nutrient supply. The cytokine storm increases capillary leak with extravasation of fluids and tissue edema and which impedes normal oxygen exchange. Endothelial cells become dysfunctional and junctions between cells weaken, enabling exaggerated inflammatory mononuclear cell migration. The accompanying inflammatory cell response can further damage arteries and organs through reduced blood and oxygen supply. The endothelium is often considered a large organ transiting throughout the arterial tree covering many miles throughout the mammalian body. When the endothelium fails the natural barriers to arterial leak and also protective mechanisms that prevent clotting and arterial occlusion are lost with resultant disseminated clotting.

Many of the cytokines that are up-regulated in acute inflammatory responses are also reported to activate the clotting (thrombotic) and clot dissolving (thrombolytic) cascades. These serine proteases in the thrombotic and thrombolytic pathways are sequentially activated

and regulated by serine protease inhibitors (serpins). Conversely, many of the thrombolytic factors such as the plasminogen activators and the clotting factors X and thrombin are also reported to activate inflammatory responses. While the inflammatory mononuclear cells, neutrophil, macrophage, and T lymphocyte responses increase arterial and organ damage due to invasion and organ damage, the role of the thrombotic and thrombolytic protease cascades in driving excess inflammation is often overlooked.

The thrombolytic plasminogen activators, urokinase- and tissue-type plasminogen activators (uPA and tPA, respectively) activate plasminogen to form plasmin that in turn dissolves fibrin clots. However, what is less well known is that uPA activates the pro forms of matrix degrading enzymes, matrix metalloproteinases (MMPs), which break down connective tissue collagen and elastin and allow cellular invasion into the arterial wall and organs. uPA and tPA also have intrinsic ability to break down fibrin. The plasminogen activators also break down connective tissues or activate growth factors such as vascular endothelial growth factor (VEGF), transforming growth factor beta (TGFβ), and basic fibroblast growth factor (bFGF) and / or release these growth factors from connective tissue stores, further activating inflammatory cell responses, and cell proliferation. uPA interacts with the uPA receptor that sits at the leading edge of invading inflammatory cells promoting cell invasion by breaking down connective tissue barriers to cell migration. The clotting factors thrombin and factor X also interact with protease activated receptors (PARs) on the cell surface of endothelial cells and inflammatory mononuclear cells and are reported to increase cytokine expression and thus again further enhance activation of the innate immune response. Serine proteases in the coagulation and thrombolytic cascades are generally regulated by serpins that represent up to 2-10% of circulating plasma proteins. Serpin regulators are also consumed in the DIC state causing further dysregulation and again excess bleeding and clotting. Thus the initial outpouring of thrombotic and thrombolytic proteases, the 'hemorrhagic hurricane', also induces inflammatory cytokine activation and the 'cytokine storm'.

Once a septic state has deteriorated to shock with DIC, there is at present no recognized proven beneficial treatment for septic shock with DIC and many agents have failed clinical testing. Treatment of the

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underlying infection is the front line of therapy but is less effective for shock and of course anti-viral agents are less available except in select viral infections. Prior trials with serpins such as anti-thrombin III, which is activated by heparin, have had reported partial efficacy in sepsis and DIC, but have proven effective only under restricted conditions, e.g. in the absence of heparin. Treatment with clotting factors and thrombolytics is also limited to septic states with ongoing excess bleeding or clotting. Similarly, while animal models and even clinical trials have suggested some benefit with steroid and anti-inflammatory cytokines, such as interleukin 10 (IL-10), these studies are inconclusive. In our research group we have recently detected improved outcomes in viral sepsis in mouse models during treatment with a virus-derived serpin that inhibits both coagulation and also thrombolytic proteases. Whether this will

translate to efficacy in clinical trials is of course unknown but again suggests that the interactions of the coagulation and inflammatory systems in lethal septic states bear further investigation. In conclusion, septic shock with associated cytokine storm and DIC is *at heart, a vascular disease*, by many criteria, a vascular disease with pathogenic disorders of the arterial endothelium, the circulating mononuclear cells and the coagulation cascade. The role of dysregulated coagulation in driving the septic shock state remains incompletely understood. The interactions between inflammatory cytokines and thrombotic and thrombolytic cascades also remain incompletely defined. We would suggest that the '*hemorrhagic hurricane*', as for the '*cytokine storm*', is associated with increased mortality in septic shock and represents an unmet therapeutic need, deserving of further investigation.