

# HDFx for the prevention and treatment of vasodilatory septic shock: A personal perspective

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## Prevention and treatment of vasodilatory septic shock

Circulatory shock is a significant and sustained loss of effective blood and plasma volume to critical key organ regions of the body, which results in a regional low-flow state, eventuating in hypoperfusion of critical peripheral tissues and organs [1]. This pathophysiological situation thus leads to deficits in transcapillary exchange and nutritive blood flows. Clinically, there are five major types of circulatory shock: hypovolemic, cardiogenic, anaphylactic, distributive, and septic [1-3].

Septic shock is often termed “a vasodilatory shock” and is a leading cause of morbidity and mortality in the USA and Europe [1-4]. Both septic and traumatic shock involve substantial fluid loss, exudation from the microcirculatory blood vessels, and increases in postcapillary permeability. Unless this situation is treated quickly, these events trigger the demise of the patient. Septic shock is often treated with catecholamines, inotropic agents, vasopressin, and corticosteroids to maintain arterial blood pressure, venous return, cardiac output, and distribution of blood to key peripheral tissues (i.e., brain, heart, and kidneys) [1-5]. Despite the use of these drugs, this often results in decreased cardiac output, intensified peripheral ischemia, and multiple organ failure, particularly of the heart, kidneys, lungs, and liver, followed by death. With the increased number of hospital-borne infections caused by “superbugs”, increased numbers of septic shock patients are becoming more and more prevalent.

A major concern in the septic shock patient are the pathological changes that rapidly take place in the postcapillary venules, tiny microscopic blood vessels usually only 20-40  $\mu$ m wide. Blood pools in these microscopic vessels due to loss of vasomotor tone, increased adherence of leukocytes, monocytes, and macrophages to the inner endothelial cells of the venules followed by release of numerous cytokines and chemokines, often leading to what is termed a “cytokine storm” [1,4,6-10]. These events give rise to a severe inflammatory component which leads to increasing morbidity and mortality. Unless these inflammatory reactions can be “curtailed very rapidly, the patient will not survive. Knowing these events, first-hand, through our studies, over a period of more than 50 years [1,10-20], we have been working on approaches to the “septic shock syndrome” that attack the problem from several points, namely:

1. The design of new molecules that can pharmacologically manipulate the microvascular arterioles and muscular venules by promoting

ceilings on vasoconstriction and restoring close-to-normal microvascular tone [10-27].

2. The design of molecules that stimulate various arms of the mononuclear phagocytic system [6,10,16,24,27-38].
3. Searching for molecules that stimulate the innate immune system to ameliorate/prevent the inflammatory responses [10,34,38-40].
4. Searching for molecules that would reduce the need for large transfusions of blood, plasma, and fluids [41-44].
5. Searching for molecules, in the body, that prevent, and stem superimposed infections caused by “superbugs” found in many hospital environments [44-49].
6. Searching for molecules that can accelerate wound healing, particularly at the microvascular level [50].

The “classical” studies of Elie Metchnikoff, in 1884, and Walter B. Cannon in the 1920's suggested that the body might produce its own powerful host-defense factor(s) to defend against infections and fluid loss [51,52]. Metchnikoff's early studies [51] pointed to the important contributions of macrophages and phagocytic leukocytes to natural (innate) resistance against pathogenic bacteria and viruses.

Over the past decade, many hospitalized patients have died of common and once treatable bacterial diseases, such as pneumonia and blood (septic) or urinary tract infections [53-59]. Nowadays, it is difficult to undertake major surgical procedures or chemotherapy without antibiotics, as more and more patients die afterwards from infections resulting in septic shock. Gram-negative “superbugs” seem to be the major culprits in many of these septic shock patient deaths [53-59]. Gram-negative bacteria are more difficult to kill than gram-positive bacteria because they are protected by “double membranes”. So, to kill the gram-negative bacteria, most of the approaches have been to design antibiotics to penetrate these membrane barriers. In our opinion, another likely approach would be to engulf the bacteria

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and digest them within “supercharged” macrophages, Kupffer cells, phagocytic leukocytes, platelets and NK cells. But for this to occur, the microcirculation to key organs, namely the liver, spleen, and lungs must perform have optimal capillary blood flows and distribution. In addition, any therapy should prevent release of cytokines and chemokines, thus preventing “cytokine and chemokine storms”. We, thus, believe an ideal drug (or therapeutic modality) needed to stem gram-negative infections and septic shock should be one that could stimulate multiple arms of the innate immune system coupled to modulation of key organ microcirculatory blood flows. To our knowledge, only HDFx appears to combine these qualities and demonstrate therapeutic attributes against several classes of bacterial “superbugs” [10,44-50]. The uniqueness of HDFx to accelerate wound healing [50] and promote tissue regeneration [50] should greatly aid treatment and recovery of patients characterized with septic shock. Its many anti-inflammatory benefits [10,44-50] should make it a required therapeutic modality in all high-risk surgical procedures.

## Conclusion

It is our belief that all patients subjected to invasive surgical procedures (with a predilection to development of septic shock) or patients in shock should be administered protective doses of HDFx prior to and after lung, heart and brain surgeries, or prolonged hospital stays.

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