

OPINION

Addressing the Complications of Ebola and Other Viral Hemorrhagic Fever Infections: Using Insights from Bacterial and Fungal Sepsis

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Introduction

Research on Ebola virus (EBOV) has focused on preventing and controlling the infection using vaccines and antiviral therapies. Given the long-term challenge of the current epidemic and the likelihood of future outbreaks of viral hemorrhagic fevers caused by the filoviruses, including EBOV and Marburg virus, efforts should also focus on developing therapies to reduce the deadly complications of infection with these viruses [1,2]. There are striking similarities in the syndromes caused by bacterial and fungal sepsis [3–14] and by EBOV [15–27] (Table 1). Sepsis, defined as the systemic inflammatory response to infection, causes a spectrum of pathology ranging from mild, basic physiologic and laboratory derangements to shock, multiple organ failure, and death [3,7]. While the term “sepsis” is generally used in the context of bacterial and fungal infections, all microorganisms, including viruses, can cause sepsis. This Opinion argues that the wealth of knowledge about bacterial and fungal sepsis (herein referred to as “classical sepsis”) should be used to inform the development of adjunctive therapies to improve the outcome of EBOV and other viral hemorrhagic fevers.

Pathophysiology of Classical Sepsis and EBOV

In classical sepsis, activation of innate immune pathways via pattern recognition receptors, such as the toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors, initiates systemic inflammation [29–31]. Maladaptive responses in sepsis cause excessive inflammation, endothelial dysfunction, coagulopathy, vascular leak, shock, and organ failure [11–13]. Analogous to the “cytokine storm” of classical sepsis, EBOV also causes systemic inflammation, endothelial dysfunction, coagulopathy, vascular leak, shock, and organ failure [17–25]. Fatal EBOV is associated with high levels of pro-inflammatory cytokines, chemokines, the anti-inflammatory cytokine IL-10, and nitric oxide [17,19,20]. Similar to classical sepsis, EBOV also causes immune suppression and a predisposition to secondary bacterial infections [11,15,23]. This latter complication has prompted the administration of empiric antibiotics to patients with EBOV [24–26]. It is possible that classical sepsis therapies may be beneficial in EBOV, in part because of their impact on the complications of secondary bacterial sepsis.



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Table 1. Similarities between Severe and Fatal EBOV and Classical Sepsis.*

Parameter	Similarities	References
Systemic Inflammation	Increased levels of pro-inflammatory cytokines (e.g., interleukin 6 [IL-6]), chemokines (IL-8), and the anti-inflammatory cytokine IL-10	Classical Sepsis: [5,10,11]; EBOV: [17,19,20]
Immune Dysfunction	Increased susceptibility to secondary bacterial infections, lymphocyte apoptosis	Classical Sepsis: [4,14]; EBOV: [23,28]
Coagulopathy	Increased D-dimers, thrombomodulin, ferritin, disseminated intravascular coagulation, thrombocytopenia	Classical Sepsis: [9,12]; EBOV: [17,18,20]
Endothelial Dysfunction	Vascular leak with hypovolemia	Classical Sepsis: [13]; EBOV: [23–25,27]
Organ Dysfunction	Renal insufficiency, hepatic dysfunction, respiratory failure, neurologic dysfunction	Classical Sepsis: [6,8,11]; EBOV: [21–25]

* Classical sepsis is defined as bacterial and fungal sepsis

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The mechanisms underlying immune and endothelial cell dysfunction and organ failure in EBOV have yet to be unraveled. Infection of monocytes, macrophages, and dendritic cells leads to acute inflammation [16]. Early activation and subsequent massive apoptosis of T-lymphocytes is associated with fatal outcomes in EBOV [17,32]. The innate immune system has been implicated in the beneficial and harmful responses to EBOV [15,27,33,34]. The EBOV glycoprotein (GP) is a putative TLR4 agonist [27,35]. The shed surface GP of EBOV has been detected in the blood during infection; it activates macrophages and endothelial cells and induces endothelial cytotoxicity and permeability [27,36]. Finally, EBOV suppresses antiviral immunity by interfering with signaling via the innate immune receptor, RIG-I, and by interfering with type I interferon (IFN) production and signaling [28,37–40]. The resultant increased viral load may further exacerbate inflammation by activating innate immune pathways and by causing cytolysis.

Defining Approaches to the Viral Hemorrhagic Fevers Based on Classical Sepsis Research

Described below are strategies that have been studied in classical sepsis and could be applicable to sepsis caused by EBOV and other viral hemorrhagic fevers (Fig 1). Recognizing that some of these strategies will not be feasible in resource-limited areas, it would nonetheless be reasonable to move forward with preclinical and clinical studies to further characterize the pathophysiology and develop approaches to reduce the complications of EBOV sepsis.

Supportive therapies

The Surviving Sepsis Campaign guidelines provide detailed instructions for the care of patients with sepsis based on state-of-the-art knowledge and therapeutics [41]. Mainstays of management include antibiotics, procedures to remove infectious foci, and the administration of basic supportive therapies (including fluids and vasopressors) to maintain tissue perfusion. More aggressive therapies are used to support patients through sepsis-induced organ failure. For example, ventilator support and renal replacement therapy are used to manage respiratory or renal failure, respectively [41]. Recent reports suggest that early administration of fluids, electrolytes, and nutrition reduces shock and organ failure in EBOV [23–26]. Thus, strong efforts should continue to be made towards making these basic therapies widely available. Although intensive care therapies such as mechanical ventilation and renal replacement therapy may not be available in all areas, they should be utilized in patients being cared for in countries with

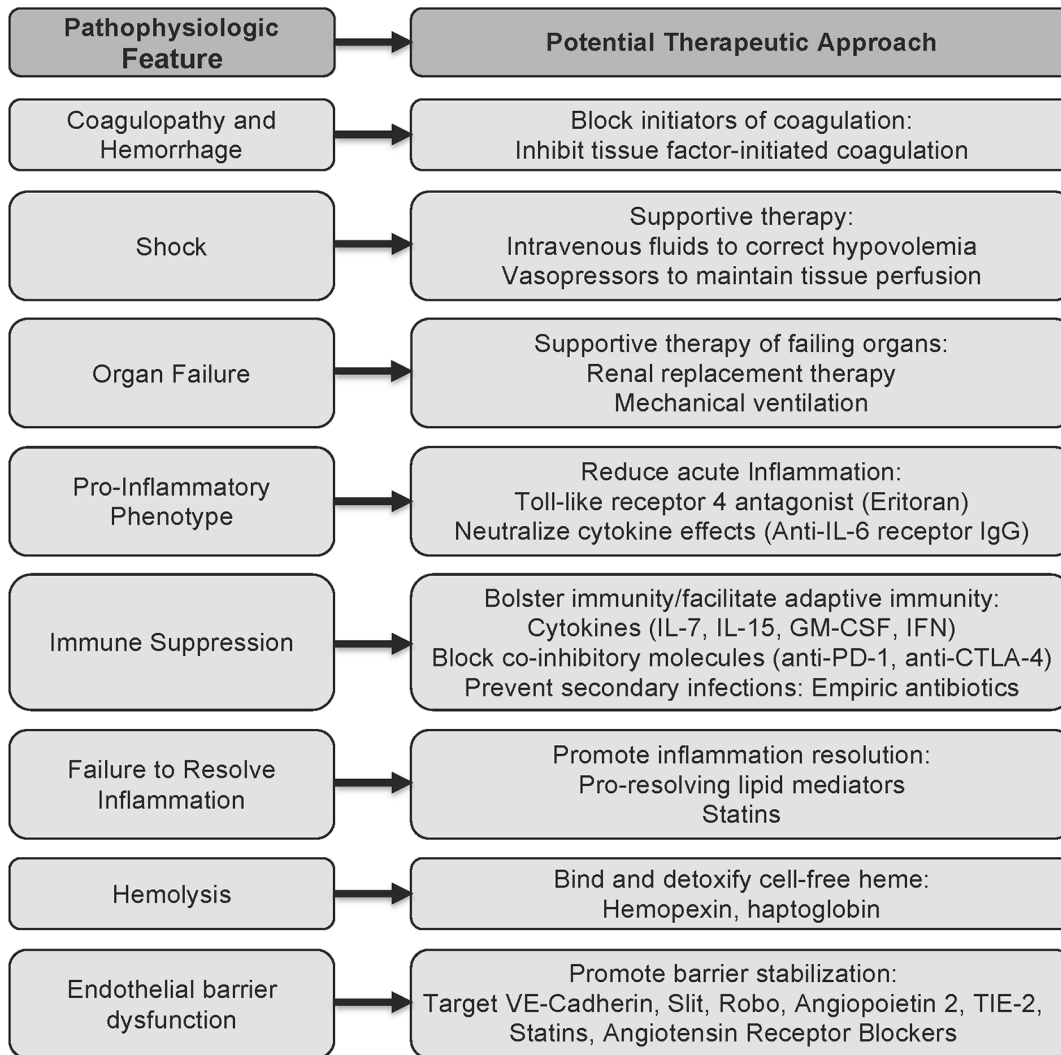


Fig 1. Potential approaches to sepsis caused by viral hemorrhagic fevers based on insights from classical sepsis. The schematic outlines potential approaches to reducing the downstream complications of the viral hemorrhagic fevers, based on what is currently known about the pathophysiology of EBOV sepsis and the state of the art of classical sepsis research.

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adequate resources, since recent data strongly suggest that these therapies improve the outcome of severe EBOV [23,25].

Reduce acute inflammation

Numerous sepsis trials have used agents to neutralize specific pro-inflammatory mediators or to block inflammatory receptors. These directions have not yet been successful in reducing the mortality of classical sepsis [42]. In contrast to the heterogeneity of classical sepsis, EBOV sepsis is caused by a single microbe whose pathogenesis follows a reasonably characteristic course. Therefore, it is conceivable that the appropriately timed administration of an agent to neutralize the effects of an inflammatory mediator could be beneficial in EBOV. In this regard, high levels of IL-6 have been reported to correlate with fatal EBOV [19], and a humanized antibody to the IL-6 receptor has been used in humans to safely treat rheumatoid arthritis [43]. However, this approach is highly speculative, as high IL-6 levels have not yet been proven to

mediate fatal outcomes of EBOV. Furthermore, although high cytokine levels correlate with fatal EBOV, paradoxically, an early robust pro-inflammatory response is associated with better outcomes in EBOV infection [32]. This observation suggests that early administration of agents to neutralize pro-inflammatory mediators such as IL-6 could, in fact, worsen outcomes by interfering with antiviral immunity and/or by increasing susceptibility to secondary bacterial infections.

One intriguing possibility would be to use a TLR4 antagonist such as Eritoran to reduce activation of leukocytes and endothelial cells. A TLR4 antagonist might reduce systemic inflammation and endothelial dysfunction induced by the EBOV-shed GP, a putative TLR4 agonist [27,35], without interfering with the initiation of protective responses via other intracellular innate immune receptors, such as RIG-I. Despite the recent negative Phase III randomized controlled trial (RCT) in classical sepsis [44], and given the safety of Eritoran in humans, it would be reasonable to study this approach in preclinical studies and to consider a limited trial in humans with EBOV.

Reverse immune suppression

Sepsis and EBOV disease cause immune suppression. Current sepsis studies are focused on restoring immune function using cytokines (e.g., IL-7, IL-15, GM-CSF, and type I IFN) or blocking co-inhibitory molecules (e.g., PD-1 and CTLA-4) [14]. Early treatment with immune-enhancing agents may promote earlier adaptive immunity and facilitate more rapid resolution of infection. This approach might be beneficial in EBOV, in which higher viral loads correlate with increased mortality [20,22].

Promote inflammation resolution

The failure to resolve acute inflammation is believed to contribute to poor outcomes in sepsis. Specialized pro-resolving lipid mediators, including resolvins, maresins, and lipoxins, can reduce inflammation without compromising anti-microbial defenses and are being investigated in preclinical sepsis studies [45–50]. The endocannabinoids, another class of endogenous lipids, have received attention recently for their ability to modulate inflammation [51–53]. The availability and safety of plant-derived cannabinoids suggests that, if effective, they could be viable treatment options. Statins have inflammation-resolving properties and have been proposed for EBOV [45,54]. However, some recent meta-analyses of RCTs have failed to show a survival benefit for statins in classical sepsis [55,56].

Corticosteroids

Following the Surviving Sepsis Campaign guidelines [41], corticosteroids could potentially be used in patients with EBOV and refractory shock. However, although low-dose corticosteroids can reverse shock, recent meta-analyses of RCTs in classical sepsis have failed to show that corticosteroids improve survival [57,58]. Based on the lack of definitive proof that corticosteroids improve outcomes in sepsis and the potential for corticosteroids to impair adaptive immunity and exacerbate gastrointestinal bleeding, their routine use in EBOV is not recommended.

Modulate coagulation pathways

The coagulopathies of classical sepsis and EBOV are initiated through activation of tissue factor [9,59]. At the extreme, these syndromes cause disseminated intravascular coagulation (DIC). The mixed coagulopathy of EBOV presents a conundrum as to whether to target coagulation, anticoagulation, or fibrinolysis. Studies in EBOV have focused on modulating proximal

coagulation pathways, which may reduce bleeding and microvascular thrombosis. Treatment with an inhibitor of tissue factor-initiated coagulation was reported to improve outcomes in nonhuman primates with EBOV, suggesting that this may be a viable approach in humans [60]. Neither activated protein C nor tissue factor pathway inhibitor (TFPI) seem appropriate for testing in EBOV based on negative RCTs in classical sepsis [61,62] and concerns that they may exacerbate bleeding.

Stabilize the endothelium

The proteins VE-cadherin, Slit, Robo, Angiopoietin 2, and TIE2—all involved in maintaining the endothelial barrier—are being explored as therapeutic targets in classical sepsis [63–65] and are potential targets in EBOV. Combined treatment with statins and angiotensin receptor blockers, which each have endothelial stabilizing effects, has also been proposed to treat the vascular leak associated with EBOV [54].

Bind cell-free heme

The syndrome of DIC causes hemolysis with hemoglobin release. Cell-free heme potentiates inflammation induced by microbial products [66,67]. Recent reports that the heme binding proteins hemopexin and haptoglobin are protective in sepsis models [66–68] suggest that these proteins could be viable adjuvant therapies for EBOV.

Concluding Remarks

Although we are encouraged by the reduction in the current EBOV epidemic, recently, cases of EBOV have been reported again in Liberia [69], and it is likely that there will be future outbreaks of EBOV and other viral hemorrhagic fevers. Numerous lives may again be lost while developing a vaccine. Insights from classical sepsis research could be used to develop approaches to address the complications of the sepsis that can be common to the viral hemorrhagic fevers. These approaches could be implemented well before a vaccine is available and could hugely impact the morbidity and mortality of EBOV and other viral hemorrhagic fevers.

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