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Therapeutic intervention in Crimean-Congo hemorrhagic fever: where are we now?

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Crimean-Congo hemorrhagic fever (CCHF), first described in 1944 in the Crimea, is a widespread tick-borne zoonosis that causes a hemorrhagic syndrome exclusively in humans, with case-fatality that can exceed 30% [1]. The causative agent, CCHF virus, a ssRNA virus in the genus *Nairovirus* within the family Bunyaviridae, is perpetuated silently in nature in a vertebrate host–tick cycle. Human infections occur through tick bite, crushing of engorged ticks or exposure to blood or bodily fluids of infected animals or CCHF patients [1]. CCHF has a short incubation period of 3–7 days, followed by a prehemorrhagic and hemorrhagic period that result in convalescence or death [2]. The disease occurs over a vast region from China through the Balkans to South Africa, closely mirroring the distribution of *Hyalomma* spp. ticks, the primary tick vector [3]. Cases are seasonal due to tick life cycle and typically occur sporadically in agricultural regions, but can also be associated with clusters of human-to-human transmission. CCHF remains one of the most clinically relevant and widespread types of viral hemorrhagic fever.

After 70 years, where are we in regards to CCHF treatment? To date, supportive care remains the mainstay of treatment. A vaccine is not available and current, widely accepted, recommendations for care of patients do not include CCHF-specific therapeutics. To identify novel CCHF treatments there is a need for both large-scale screening of candidate

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compound libraries, and a targeted approach founded on knowledge of disease pathogenesis. Ribavirin, a nucleoside analog, was tested as a potential CCHF treatment and demonstrated efficacy against CCHFV in cell culture and animal studies [4,5]. However, the clinical efficacy of CCHF remains controversial. The utility of ribavirin in CCHF is highly debated, with reported success dependent on study design [6]. Additionally, the timing of administration appears to be critical, with treatment required early in the course of disease for beneficial effects. As a result, ribavirin may not be the most suited for the majority of identified cases due to the acute nature of the disease. Furthermore, to determine a true measure of ribavirin effectiveness for CCHF would require a placebo clinical trial with significant inherent ethical issues. Many other RNA-virus inhibitors exist as candidates for CCHF treatment. It is important to move past the ribavirin debate and focus on detailed screening of additional candidate therapeutics. Another broad-spectrum RNA virus inhibitor, favipiravir, has promising results both *in vitro* and *in vivo* that support continued investigation for CCHF use [7]. Ultimately, suitable candidates will require rigorous *in vitro* and *in vivo* testing, supported with clinical trials. The efficacy of top candidates must be thoroughly demonstrated, in well-designed and controlled studies, to prevent another CCHF clinical debate, as that seen with ribavirin.

A targeted approach would be based on the pathogen or the host cell response to infection, including cellular targets preventing entry or preventing cleavage required for virus propagation, such as the use of a SKI-1 inhibitor [8]. Other targeted approaches include immune modulatory strategies. Clinical aberrations in the host inflammatory response suggest that inappropriate immune responses, magnitude and or timing of both inflammatory and anti-inflammatory responses, contribute to disease severity and fatal outcome [9]. Increases in inflammatory cytokines are well described in CCHF; however, the ability to correlate levels with a particular outcome is not consistent across clinical studies. Of the cytokines described, TNF- α levels appear to be the most consistent as a positive correlate of disease severity [9,10]. Interpreting levels of other cytokines in regards to prognosis, including IL-6, IL-10 and IL-12 are less clear [9]. In addition, elevated neopterin, produced by macrophages and DCs upon stimulation by interferons (IFNs), used as a tool to assess intensity of cell-mediated immunity, has been described in severe CCHF [11]. However, both the innate and adaptive immune responses also appear to be involved in protection; the only lethal animal models to date for CCHF are those lacking functional innate immune responses, and weaker antibody responses have been associated with increased viral load and poor outcome [1,12].

Treatments to consider include IFN or immunoglobulin therapy. Pretreatment of cells with IFN demonstrated a dose-dependent effect. *In vitro*, IFN has no significant activity against a pre-established CCHFV infection [13]. Testing of IFN treatment has never been performed *in vivo*, and the utility of postexposure treatment in a CCHF patient remains unknown. Monoclonal antibodies have been developed specific to the glycoproteins (Gn and Gc) [14], but measures of virus neutralization *in vitro* did not necessarily correlate with protection against illness or death *in vivo*, suggesting a complex interplay of antibody properties and host factors. Use of intramuscular and intravenous anti-CCHF immunoglobulin treatment from convalescent patients have been reported from the former Soviet Union, South Africa,

Turkey and Bulgaria, and in the latter it remains in use. However, none of the studies reviewed in Keshkar-Jahromi *et al.* adequately supported efficacy of specific immunoglobulin for postexposure prophylaxis or treatment of CCHF, because of the lack of proper controls, preventing sound conclusions [6]. Ultimately, targeting CCHFV using an immune modulatory strategy requires a significantly improved understanding of disease pathogenesis. Given the evidence supporting the likelihood of an immunopathogenic basis to disease, we must first understand the specific mechanisms of the host response, pathogenic and protective, and their respective occurrences in the course of disease. A successful immunology approach to therapeutics will require appropriately timed, evidence-based immunostimulation and immunosuppression. While knowledge of predictive parameters and biomarkers for disease severity has improved with increased access to case-patient clinical data over the last decades, the pathogenesis of CCHF is still poorly understood. Endemic areas with hundreds of cases per year such as Turkey or Iran represent a continued opportunity for data acquisition in pathogenesis studies.

The development of CCHF therapeutics is certainly warranted; in endemic regions, cases can number upwards of 1000 annually [1]. Cases are often sporadic and present typically in remote or low-infrastructure areas. The current standard of care for CCHF patients is supportive care with or without nonspecific antiviral treatment in the form of ribavirin. An emphasis must be placed on continued assessment of the most clinically effective supportive treatment options for CCHF and promoting the appropriate health care infrastructure to provide this care. Supportive care is relatively easy to provide, and likely accessible in a basic care setting. Supportive care includes diligent monitoring of patient complete blood counts, clinical chemistry and blood pressure, management of fluid and electrolyte balances, addressing bleeding foci and avoiding taxing the coagulation response. Supportive care may also include frozen plasma or platelets to manage abnormalities associated with impaired hemostasis, crystalloid and colloid infusions for management of hypovolemic shock, and respiratory support [6,15].

Advancements in CCHF research and therapeutic development have been slow due to several issues including BSL-4 biocontainment requirements in many countries, and a relatively small research community focused on CCHF. Acquisition of clinical data is not always feasible, and gross and histopathological findings reported from human cases are limited. The situation is further complicated by the fact that laboratory studies investigating basic questions of CCHF pathogenesis have been hindered by the lack of a suitable animal model to better investigate disease *in vivo*, and correlate *in vitro* findings to multisystem models of disease. CCHFV is a challenging virus to work with; virus isolation requires strict sample maintenance in cold chain, cytopathic effect is only seen in select cell lines and high-titer virus stocks are difficult to generate. Additionally, in contrast to other bunyaviruses, CCHFV has complex glycoprotein processing, involving several viral protein intermediates with unknown clinical implications. There have, however, been several important advances in CCHF research that will undoubtedly aid in the hunt for novel therapeutics. Animal models have now been characterized. While all known to date are immunocompromised, they are still sufficient for use as *in vivo* therapeutic screening tools. Importantly, a reverse genetics system for detailed molecular characterization of relevant viral mediators of disease

and strain-specific pathogenicity has recently been developed [Bergeron *et al.*, Unpublished Data].

In addition to the use of novel therapeutics, there are other approaches to disease control that must be considered that do not rely on advancement in disease knowledge or access to appropriate biocontainment facilities for either *in vitro* or *in vivo* characterization. Ticks are not only the vector but also the reservoir for CCHFV since they potentially transmit the virus not only to the next life stage but also to the next generation. A One Health approach that recognizes that the health of humans is connected to the health of animals and the environment, in which key amplifying hosts are vaccinated against CCHFV together with acaricide treatment, could dramatically reduce amplifying host infection, ideally undermining regional tick maintenance of virus in nature. Current disease and therapeutic knowledge emphasize that early recognition of CCHF will be essential in improving disease outcome. Importantly, it will allow for the much-needed acquisition of additional clinical data. Ultimately, the health-care community and research community must develop a united front to share information and move forward to develop clinically feasible and relevant intervention strategies.

Biographies



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