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Therapeutic Approaches for New World Hantaviruses

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Opinion statement

New World Hantaviruses are characterized by a fairly non-specific viral prodrome, usually followed by a precipitous decline in cardiopulmonary function leading to circulatory collapse and multiorgan failure. Combined with a sporadic nature and unclear epidemiology, the development and use of specific treatments for Hantavirus infection are difficult. The underpinning of any therapeutic approach to Hantavirus disease is providing supportive care long enough for the elaboration of a curative immune response on the part of the patient. At this time, this is best accomplished by a combination of clinical acumen for the recognition of the chief risk factor, namely exposure to rodent excreta, combined with early referral and transfer to a clinical centre capable of providing advanced cardiopulmonary

support. Several additional therapies are currently under investigation, ranging from antiviral drugs to convalescent serum. While these offer some early promise, none of these will be able to replace aggressive cardiopulmonary support in the foreseeable future.

Introduction

New World Hantaviruses constitute a relatively novel group of viral pathogens. While the non-pathogenic Prospect Hill virus was the first New World Hantavirus to be identified in 1983 [1], it was not until 1993, following an outbreak in the Four Corners region of the USA [2], that these pathogens became recognized as a public health concern. Members of the *Bunyaviridae* family, Hantaviruses, have been found to be the causative agents of two distinct clinical syndromes. Old World Hantaviruses, which include Hantaan virus, Dobrava-Belgrade virus and Seoul virus, amongst others, cause hemorrhagic fever with renal syndrome (HFRS) [3, 4•, 5], while Puumala virus causes nephropathia epidemica, a milder form of HFRS [5]. These viruses are mainly distributed in Europe and Asia, with recent detection in Africa [6]. In contrast, New World Hantaviruses, which include Sin Nombre virus and Andes virus, cause Hantavirus cardiopulmonary syndrome (HCPS), also referred to as Hantavirus pulmonary syndrome [7]. HCPS has a higher mortality rate than HFRS (35 versus 10 %) [5] and, as the names imply, have very different target organs. This review will focus solely on the management of HCPS. Over 700 cases of HCPS have been documented in Canada and the USA with several hundred more identified in Central and South America [8, 9]. All Hantaviruses known to date are transmitted by exposure to the secretions of the natural rodent host reservoir [4•]. Transmission is most efficient when individuals are in enclosed spaces with limited ventilation, such as attics or outbuildings colonized with rodents [4•].

HCPS is characterized by a fairly prolonged incubation period, averaging 2 weeks but ranging from 1 to 6 weeks [5]. A recent report has suggested the incubation period could perhaps be longer [9]. The initial phase of the disease is very non-specific, characterized by an influenza-like illness lasting 3–5 days. This prodromal phase is usually followed by an acute phase characterized by very rapid deterioration in cardiac and pulmonary function over a 24–48-h period [5, 7, 10•]. Diagnosis requires a high index of suspicion in the context of a risky exposure and an appropriate clinical progression [11]. Hantavirus specific testing is usually available through reference laboratories in the form of serologic and/or molecular testing [5, 7]. Person-to-person transmission has only been described for Andes virus and was felt to be inefficient, such that only household or very close contacts were deemed at significant risk [12].

Management options for HCPS are fairly limited at this time. The mainstay of therapy remains early recognition of the disease and rapid implementation of aggressive supportive care. Specific areas requiring particular attention based on the typical clinical syndrome of HCPS include monitoring for and correcting the following: respiratory compromise, myocardial dysfunction, significant hemoconcentration, and thrombocytopenia [5, 7, 11]. A few specific therapeutic options, such as high-dose steroids and ribavirin, have been tried in small-scale trials. These specific therapies, either effective or not, are discussed further under their appropriate heading.

Treatment

Diet and lifestyle

- The chief risk factor for infection by New World Hantaviruses is exposure to the secretions of infected rodents [4•]. While modification in diet or lifestyle has little to no bearing on survival from infection once it occurs, avoidance of exposure is the key public health measure. Public

health organizations in areas with known or presumed presence of Hantavirus vectors should focus on educating local populations about ways to mitigate risk, such as proper use of personal protective equipment and personal hygiene.

Pharmacologic treatment

- At this time, there are no medications that are approved specifically for the treatment of New World Hantaviruses.
- There are two general drug modes of action that have been assessed in small trials.

  – **Immune Modulation:** aimed at the presumptive pathophysiology of HCPS, which may have an immune dysregulation component
  – **Antivirals:** aimed at interfering with the Hantavirus replication cycle
- A challenge facing clinicians interested in trying newer antivirals (such as favipiravir) may be the availability of these drugs. Animal data suggest that most antivirals to date are best when administered prior to the onset of the cardiopulmonary phase of the disease [13, 14, 15•]. The challenging nature of Hantavirus diagnosis combined with a narrow therapeutic window and uncertain drug availability may make antiviral use difficult

Immune modulation

Methylprednisolone

The pathogenesis of Hantavirus diseases is still unclear; however, there has been a strong suggestion that disease is, at least in part, related to inappropriate immune activation [10•, 16]. This observation has led to interest in using immune modulation as a therapy, keeping in mind the need to balance potential benefits with the risk of acute immune suppression in the context of a viral infection. High-dose intravenous methylprednisolone (16 mg/kg/day; maximum 1000 mg) for 3 days was assessed in a randomized, double-blind study involving 60 confirmed cases of Andes virus-induced HCPS in Chile. The study demonstrated no benefit in the treatment group based on a composite endpoint (mortality, low PaO2/FiO2 ratio, cardiac index ≤2.2 L/min/m^2, pulseless electrical activity, ventricular tachycardia or fibrillation) [17••]. This same study demonstrated no significant harm from the intervention, including no increase in viral load. In contrast, an earlier retrospective review of 22 HCPS patients had demonstrated some benefit [18]. While the RCT reported by Vial et al. [17••] represents a small sample size, given the rarity of the disease, it provides the best quality evidence currently available. Based on these data, we cannot recommend the use of high-dose methylprednisolone at this time.

Antivirals

Ribavirin

Ribavirin (1-β-D-ribofuranosyl-1,2,4-thiazole-3-carboxamide) is a broad-spectrum antiviral compound active against a wide range of both DNA and RNA viruses. Its primary mechanism of action is not completely understood but may be related to its role as a guanosine analogue involving the inhibition of the inosine monophosphate dehydrogenase (IMPDH) enzyme, direct inhibition of the viral RNA polymerase and/or lethal RNA mutagenesis [19]. Ribavirin demonstrates activity against Hantaviruses in vitro and in animal studies [13, 15•]. Human studies have been disappointing regarding the use of ribavirin for HCPS [20••, 21]. These studies have been complicated by small sample sizes and difficulty accruing patients. A recent meta-analysis of the human and animal data revealed that ribavirin was effective for HCPS in animal models but not in humans [22]. The reason for the inconsistent findings is perhaps best theorized based on work by Safronetz et al., which demonstrated in hamsters that ribavirin was 100 % effective when initiated up to 3 days post infection, but rapidly became ineffective from day 5 post infection onward [15•]. The authors postulate that ribavirin may only be effective when initiated very early during the systemic replication phase of the virus. The hamster model of disease simulates human disease well in the sense that a long latent phase (7–8 days in the case of hamsters) is followed by precipitous decline and death within 24–48 h of the onset of signs of infection [23]. Since humans presenting for care with HCPS are usually in the declining phase of their illness and likely well beyond the early systemic replication phase of the virus, it is conceivable that administration of ribavirin has already lost its potential benefits [5]. At this time, use of ribavirin in the treatment of symptomatic HCPS patients is unlikely to be of benefit. In the context of an outbreak [24] or known exposure, such as a laboratory worker [25] or a group sharing a common risk factor (e.g. cleaning a Hantavirus-contaminated space) [26, 27], the initiation of ribavirin early in the disease course should be considered based on the available animal data.

Standard dosage	Trial dosage: 33 mg/kg (max 2 g) IV loading dose followed by 16 mg/kg (max 1 g) q6h IV for 4 days followed by 8 mg/kg (max 500 mg) q8h IV for 3 days [20••]
Contraindications	Considered a pregnancy category X agent due to teratogenicity in several species; effective contraception for patients for 6 months following cessation of therapy is recommended
Main drug interactions	Interacts with some antiretrovirals; may inhibit warfarin
Main side effects	Hemolytic anaemia (rare in acute treatment phase, nearly universal after 4 weeks); hypocalcemia and hypomagnesemia are reported with IV administration
Special points	Unlikely of benefit in symptomatic HCPS; potential benefit in early disease and/or known exposure event
Cost/cost-effectiveness	Cost effectiveness analysis not possible; however, ribavirin drug cost is low

Favipiravir (T-705)

	Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is a new antiviral drug whose mechanism appears to be related to competition with purine bases during RNA synthesis, leading to inhibition of the viral RNA polymerase and/or causing lethal mutagenesis upon incorporation. It has shown in vitro activity against a wide range of RNA viruses. While still deemed experimental, the drug is relatively advanced in its development cycle, having undergone phase II and III trials for the treatment of influenza [28]. With respect to Hantaviruses, favipiravir demonstrated at least equivalent and perhaps superior in vitro activity compared to ribavirin [14, 28]. There are currently no human data for use of favipiravir in HCPS. A recent study using a lethal hamster model of New World Hantavirus (Andes virus and Sin Nombre virus) demonstrated significant gains in survival when animals were treated with 50 mg/kg/day (67 % survival) or 100 mg/kg/day (100 % survival) when treatment began one day postinfection. Low dose treatment (≤20 mg/kg/day) as well as delayed treatment (≥ day 5 post-infection) proved ineffective (0 % survival) [14]. Based on body surface area conversions, the 100 mg/kg/day hamster dose translates to 14 mg/kg/day in humans. Assuming a 70 kg adult, this dose is similar to the high-dose arm of a recent dose-finding study in uncomplicated influenza (ClinTrialsID NCT01068912). Given the experimental nature of the drug and the lack of efficacy beyond 4 days post-infection, it appears unlikely that favipiravir represents a practical treatment option at this time. The animal data provide some suggestion of efficacy, and further research into this compound for human cases of New World Hantaviruses would be helpful.
Standard dosage	N/A; study dosage translates to approximately 14 mg/kg/day
Contraindications	Unknown; drug generally well tolerated but limited data; should be avoided in pregnancy unless anticipated benefit outweighs potential risks to the mother and fetus.
Main drug interactions	Unknown
Main side effects	Unknown
Special points	Drug currently only available on an investigational/compassionate release basis
Cost/cost-effectiveness	Drug not currently commercially available

Other treatments

Human plasma from survivors

The use of survivor plasma first showed promise in the Syrian hamster animal model of Hantavirus [29]. Based on these data, an open label, non-randomized trial was undertaken in Chile to evaluate the use of survivor plasma in the treatment of HCPS caused by Andes virus. A total of 29 confirmed cases were enrolled and treated, resulting in a 14 % case fatality rate. This was compared to 32 % mortality in patients not treated with survivor plasma who presented to non-study sites elsewhere in Chile [30]. Together with the animal data, the use of immune serum appears to be a potentially useful therapy.

There are, however, several important limitations to survivor plasma as therapy. First, given the wide variety of Hantaviruses with strong regional variation, collection of geographically relevant plasma would be important. Developing a pool of plasma donors is logistically complex, especially in relatively low incidence areas. The quality and infectivity-reducing abilities of antibodies also vary significantly person-to-person, making dosing challenging. Finally, human plasma is a blood product, with the inherent safety challenges involved. Since the non-randomized data are promising but not definitive, it is difficult to justify the significant costs and logistical challenges involved in maintaining a bank of immune serum at this time. Further research into a more reliable, perhaps recombinant product, appears warranted.

Extracorporeal membrane oxygenation (ECMO)

The pathophysiology of HCPS is one of precipitous cardiopulmonary collapse. This pattern makes the use of extracorporeal membrane oxygenation (ECMO) an attractive therapeutic option to support the patient long enough to allow immune system activation and clearance of the virus. Wernly et al., from the Four Corners endemic region of the southwestern USA, published a single-centre, retrospective review of their experiences with managing HCPS using ECMO [31••]. This series included 51 patients, who were treated using two slightly different strategies. The first strategy involved cannulation and initiation of ECMO following cardiopulmonary collapse, while the second strategy involved anticipatory insertion of vascular access while the patient was relatively well in order to facilitate ECMO cannulation later on. Criteria for ECMO included the following: (a) clinical presentation consistent with HCPS, (b) cardiac index less than 2.0 l/min/m^2 and (c) one of: serum lactate >4.0 mmol/L, PaO2:FiO2 ratio of <60 or cardiopulmonary deterioration.

Using these criteria, patients were felt to have a 100 % expected mortality rate without ECMO. The mortality rate in the study was 33.3 % (17 of 51 patients), demonstrating a significant survival advantage in the ECMO-treated group. Patients treated using the anticipatory vascular access strategy had better survival (80 % compared to 54 %, p=0.048).

Standard procedure:	Venoarterial approach (venovenous approach would not be appropriate due to both cardiac and pulmonary failure in HCPS)
Contraindications:	ECMO contraindications vary; in the present study, pre-existing neurologic injury, mechanical ventilation lasting more than 5 days and multi-organ failure were used as exclusion criteria
Complications:	Short-term complications occurred in approximately 35 % of patients, ranging from severe bleeding (12/51) to lower leg amputation due to ischaemia (2/51). Long-term complications in the survivors were not presented.
Special points:	Requires access to a centre with ECMO capabilities
Cost/cost-effectiveness:	The cost of ECMO support varies from institution to institution but is generally very expensive. At this time, however, ECMO provides the best survival advantage for HCPS, making it cost-effective

Emerging therapies

- Therapeutic strategies for Hantaviruses are currently an area of active research.
- The recent development of improved animal models, including a non-human primate model of Sin Nombre Virus, is likely to provide improved therapeutic candidate testing platforms.
- The headings below contain a very brief overview of potential future therapeutic options; none are presently ready for human use and are included for interest only.

New antiviral agents

A variety of novel antiviral agents under investigation have demonstrated in vitro and some in vivo activity against New World Hantaviruses. These include nucleotide analogues such as 1-beta-D-ribofuranosyl-3-ethynyl-[1,2,4]triazole (ETAR) as well as N^1-aryl purine derivatives [32, 33]. Another promising branch includes drugs that block $\alpha_v\beta_3$ integrin, thus blocking the entry of the viruses into their target cells. While several in vitro studies with promising results exist for this class of compounds, animal data are not currently available [4•].

Non-human antibodies

There currently are no licensed commercial antibody products that specifically target Hantaviruses. Some preliminary animal work has demonstrated that polyclonal antibodies elaborated by ducks vaccinated against Hantavirus were able to protect hamsters from lethal challenge with Andes Hantavirus [34]. Hamsters were 100 % protected if the antibodies were administered up to day 8 post-infection, with a drop in efficacy thereafter. Another study used transchromosomal bovines (a genetic process by which cattle are vaccinated to produce chimeric antibodies containing the human γ heavy chain and bovine κ light chains as a source of neutralizing antibodies). In that study, antibodies collected from bovines vaccinated with a DNA vaccine against Andes and Sin Nombre viruses showed protection of hamsters (7/8 and 5/8, respectively) when administered 5 days post-challenge [35]. These findings raise the possibility that monoclonal antibodies might provide therapeutic options in the future, which would circumvent the logistic challenges associated with survivor plasma. Unfortunately, these products will not be available in the foreseeable future.

Vaccines

There are several formulations of vaccines developed for Old World Hantaviruses currently in use in Asia [36]. Vaccines against New World Hantaviruses are not quite as advanced though several vaccine platforms are currently under development. The most advanced include polyvalent DNA-based vaccines which include targets for both New and Old World Hantaviruses. While some phase 1 work [37–39] has been published, these

vaccines are not yet commercially available. Additionally, experimental vaccines have not been tested in the context of post-exposure prophylaxis in animals, making their utility in a therapeutic context uncertain. Once available, a vaccine against Andes Hantavirus may have a niche role in the vaccination of contacts of an infected patient, given the possibility of human-to-human transmission of that particular virus.

Small interfering RNA

siRNA (small interfering RNA) is a newer therapeutic strategy whereby short segments of RNA bind to viral RNA and prevent transcription. Some preliminary in vitro work has shown promise in reducing viral replication in various cell lines [40].

Paediatric considerations

- There are very limited data available regarding the clinical course and management of paediatric patients with HCPS [41, 42]. This may be due to either mild and/or atypical disease in children that goes unrecognized or a relative lack of exposure to the host vectors' secretions. From the limited data available, it would appear the clinical progression is similar to that of adults, with perhaps higher mortality in adolescents (small numbers) [41]. Early, aggressive supportive care and rapid transfer to an ECMO capable facility would likely be optimal [41].

Compliance with Ethics Guidelines

Conflict of Interest
Guillaume Poliquin declares that he has no competing interest.
Mike Drebot declares that he has no competing of interest.
Allen Grolla declares that he has no competing interest.
Shane Jones declares that he has no competing interest.
Bryce Larke declares that he has no competing interest.
James Strong declares that he has no competing interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by the author.

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