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Review

South American Hemorrhagic Fevers: A summary for clinicians

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ABSTRACT

Objectives: This article is one of a series on acute, severe diseases of humans caused by emerging viruses for which there are no or limited licensed medical countermeasures. We approached this summary on South American Hemorrhagic Fevers (SAHF) from a clinical perspective that focuses on pathogenesis, clinical features, and diagnostics with an emphasis on therapies and vaccines that have demonstrated potential for use in an emergency situation through their evaluation in nonhuman primates (NHPs) and/or in humans.
Methods: A standardized literature review was conducted on the clinical, pathological, vaccine, and treatment factors for SAHF as a group and for each individual virus/disease.
Results: We identified 2 treatments and 1 vaccine platform that have demonstrated potential benefit for treating or preventing infection in humans and 4 other potential treatments currently under investigation.
Conclusion: We provide succinct summaries of these countermeasures to give the busy clinician a head start in reviewing the literature if faced with a patient with South American Hemorrhagic Fever. We also provide links to other authoritative sources of information.

Introduction

South American Hemorrhagic Fevers (SAHF) are a group of zoonotic viral infections present in South America, which have the potential to cause severe illness leading to organ dysfunction, bleeding, and death. The New World arenaviruses (NWA) responsible for SAHF include 5 out of the 8 Clade B *Mammarenaviruses* (infecting mammals) (Sarute and Ross, 2017). [Table 1] *Mammarenaviruses* frequently cause nonpathogenic, persistent infections with chronic viremia in rodent hosts/reservoirs; leading to spreading of the virus through urine, feces, and saliva to other rodents [Table 2].

Transmission to humans occurs by direct contact with infected rodents and their environment. Although bites have been described, the most common form of exposure is by the inhalation of rodents' urine and feces or direct contact with excreta/secreta through abraded skin, when human activities overlap with the rodent's natural habitat (Sarute and Ross, 2017). Household and nosocomial person-to-person transmission, as well as laboratory-acquired infections, have also been described. Rarely, sexual transmission has been described (Briggiler et al., 1987; Enria et al., 2011).

To date, only Junin virus (JUNV), the etiological agent of Argentine Hemorrhagic Fever (AHF), has a licensed prophylactic countermeasure: Candid #1, an attenuated virus vaccine developed collaboratively between the Argentine government and US military. Despite the introduction of the Junin virus, immunizations to at-risk populations in Argentina in 1991 and the incorporation of the vaccine in the Argentine National Immunization Calendar (free) in 2007, sporadic cases of AHF are still reported. While an average of 450 cases were diagnosed annually before 1991, since the incorporation of vaccination cases have been decreasing, there were only 13 confirmed cases reported in 2018 (Maiztegui et al., 1998; Feuillade, 2005; Ambrosio et al., 2011). Bolivia reported a small outbreak of Bolivian Hemorrhagic Fever in

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Table 1
New World Arenavirus (NWA).

NWA Clade	A	B	C	D (tentative)
Virus	1- Flexal 2- Parana 3- Pichindé 4- Allpahuayo 5- Pirital	1- Guanarito 2- Amapari 3- Cupixi 4- Sabiá 5- Chaparé 6- Tacaribe 7- Junín 8- Machupo	1- Latino 2- Oliveros	1- Whitewater Arroyo 2- Bear canyon 3- Tamiami
Reservoir	1- Oryzomys sp. 2- Oryzomys angouya 3- Oryzomys arbigularis 4- Oecomys paricola 5- Sigmodon alstoni	1- Zygodontomys brevicauda 2- Neacomys guianae 3- Unknown 4- Unknown 5- Unknown 6- Artibeus jamaicensis 7- Calomys musculinus 8- Calomys callosus	1- Calomys callosus 2- Neocromys benefactus	1- Neotoma albigula 2- Neotoma macrotis 3- Sigmodon alstoni
Country	1- Brazil 2- Paraguay 3- Colombia 4- Peru 5- Venezuela	1- Venezuela 2- Brazil 3- ? 4- Brazil 5- Bolivia 6- Venezuela 7- Argentina 8- Bolivia	1- Bolivia 2- Argentina	1- USA, New Mexico 2- USA, California 3- USA, Florida
Ability to cause infections in humans	No * Flexal virus has been associated with a febrile, non-fatal laboratory-acquired human infection	Yes * * 5 out of the 8 species have been known to infect humans	No	No

early 2019 and Venezuela still reports sporadic cases of Venezuelan Hemorrhagic Fever in endemic areas. Cases of Brazilian Hemorrhagic Fever and Chaparé Hemorrhagic Fever are rare, with less than 10 reported cases of each in the literature.

Because of the decrease in the number of cases of SAHF, the availability of convalescent plasma, effective for the treatment of AHF (Enria et al., 2008), for the management of Junín virus and Machupo virus infection has become scarce. Ribavirin has been used for Junín virus, Sabiá virus, and Machupo virus infections; however, efficacy has not yet been established. At least 2 other treatments, favipiravir and monoclonal antibodies, are under investigation and have shown promising results. All hemorrhagic fever-causing Arenaviruses have been classified as category A pathogens according to the NIAID-emerging pathogens scheme and require biosafety level (BSL) 4 precautions for research within the United States.

For the purpose of the article, we will use the International Committee on Taxonomy of Viruses (ICTV) 10th report for virus abbreviation (Viruses, 2018). Junin virus will be abbreviated as JUNV, Sabia virus as SBAV, Chapare virus as CHAPV, Guanarito virus as GTOV, and Machupo virus as MACV. When referring to disease names, AHF will refer to disease caused by JUNV, Venezuela Hemorrhagic Fever (VHF) caused by GTOV, Brazilian Hemorrhagic Fever (BrHF) caused by SBAV, and Bolivian Hemorrhagic Fever (BHF) as caused by MACV. Disease caused by CHAPV will be abbreviated as CHAPV-HF.

This article is one in a series of planned articles on the management of severe diseases caused by emerging viruses. Viruses were selected by the members of the Medical Countermeasures Working Group of the Special Pathogens Research Network (SPRN) within the National Emerging Special Pathogen Training and Education Center (NETEC). The NETEC is funded by the Assistant Secretary of Preparedness and Response and the Centers for Disease Control and Prevention to improve public health and healthcare systems in the United States, to respond effectively to individuals infected with suspected or confirmed special pathogens. Criteria used to select the pathogens included the following: relative rarity of the diseases and severity of the illnesses they cause, their potential to cause large-scale outbreaks, the potential need for specialized infection control management based on their historic ability to cause nosocomial infection in the hospital or field setting, and their paucity or lack of licensed countermeasures.

Following the publication of this article, updated information on the management of SAHF will be made available on the NETEC website: www.netec.org.

Methods

We summarize here the recent published literature specific to SAHF, in an attempt to provide a practical list of potential

Table 2
New World Arenavirus- Clade B- Distribution and Reservoir.

New World Arenavirus	Country	Reservoir	Described Infections in Humans
Junín virus	Argentina	*Calomys musculinus*,*Calomys laucha*, *Akodon azarae*, *Orizomys flavescens*	Yes- First isolated in 1958
Chaparé virus	Bolivia	Unknown	Yes- First isolated in 1960
Machupo virus	Bolivia	*Calomys callosus*	Yes- First isolated in 1963
Tacaribe virus	Venezuela	*Artibeus jamaicensis* (bat)	Febrile, nonfatal laboratory-acquired infections
Guanarito virus	Venezuela	*Zygodontomys brevicauda*	Yes- First recognized in 1989
Sabiá virus	Brazil	Unknown	Yes- First isolated in 1990
Amapari virus	Brazil	*Neacomys guianae*	Not yet described
Cupixi virus	Unknown	Unknown	Not yet described

countermeasures in development, in case there is an urgent need to treat a patient with one of these diseases. These are summarized in a succinct form for the ease of reference in the accompanying table.

The review involved a MeSH (National Center for Biotechnology, 2019) search string (customized for SAHF) and divided the therapeutic evidence into categories: preexposure prophylaxis, postexposure prophylaxis, treatment, infection prevention and control, and diagnostics. We then conducted title, abstract, and full text reviews of appropriate manuscripts, reviews, and book chapters. Bibliography scans were also completed on review articles and meta-analyses.

Clinical features

Incubation period

Estimated to be between 3 and 21 days (shorter in cases of laboratory exposure and longer when exposed to rodent excreta). The AHF incubation period has been reported as 6-14 days, BHF 3-16 days, VHF up to 19 days, and BrHF 6-21 days (Salas et al., 1991; Barry et al., 1995; de Manzione et al., 1998; Gomez et al., 2011; Patterson et al., 2014). The incubation period for CHAPV-HF is unknown. It used to be commonly believed that exposure to hemorrhagic fever-causing arenaviruses would consistently lead to disease; however, recent sampling of endemic-area residents has shown the presence of IgG antibodies against MACV in people who have never manifested the disease (Patterson et al., 2014; Sarute and Ross 2017; MacDermott and Ksiazek, 2018).

Pathogenesis

The exact pathogenetic mechanisms involved in NW arenaviral infections have not been fully elucidated but studies have shown that they suppress early immune responses after infection but later trigger a massive inflammatory response as disease progresses (Sarute and Ross, 2017). Infection, in animals, first occurs in pulmonary macrophages and SAHF viruses are noted in the tracheobronchial lymph nodes on pathology samples day 5 postexposure (Bell et al., 2016). Macrophage and dendritic cells appear to be the main sites of replication for the JUNV and presumably other NW arenaviruses (Sarute and Ross, 2017). A more complete explanation of cellular mechanisms of infection can be found in the literature but is beyond the scope of our purposes in this review (Grant et al., 2012; Shao et al., 2015). In the following section, we attempt to summarize important microbiological processes that may be targets for therapy or prophylactic countermeasures.

Arenaviruses have a single glycoprotein (GP) on the surface of virions, which attaches to the host cell through the transferrin receptor 1 (TfR1). TfR1, a highly conserved cell surface receptor for iron-bound transferrin uptake into cells, is the primary site of entry for these viruses (Coffin, 2013). A small number of mutations at specific amino acid positions in host TfR1 may drastically alter the infectivity of SAHF viruses. Variability of this sequence may play a critical role in the infectivity of SAHF viruses and modulation of TfR1 viral binding and is an area of further investigation for potential therapeutic interventions. Key coreceptors may also serve as target sites for the development of fusion and entry inhibitors as medical countermeasures against SAHF although other receptors, including voltage-gated calcium channels, are used as entry points in infection, and may likewise offer potential therapeutic targets (Sarute and Ross, 2017).

The TfR-1 receptor is widely expressed in a multitude of cell types, particularly highly proliferative ones such as lymphocytes, mucosal cells, and cell lines within the bone marrow. Infection of these cell lines may account for some of the gastrointestinal and mucosal symptoms and cell line depression typical of SAHF virus infection. The ability to infect cells using this highly conserved cell surface receptor leads to effects in multiple organ systems. This has been confirmed in animal pathology studies, which show that while infections due to SAHF viruses initially begin in the lymphoid tissue; MACV first infects macrophages in the tracheobronchial lymph node, with viral antigen first detectable on day 5 postexposure on guinea pig models (Bell et al., 2016). Viral antigen was detected throughout the lymphoid system by day 9 postexposure, followed by prominent spread within epithelial tissues and then the brain (Bell et al., 2016). MACV virus was isolated in multiple tissue samples 5-12 days after initial infection and correlates with widespread pathological tissue damage. Gross pathological findings in the above animal models included congestion and hemorrhage of the gastrointestinal mucosa and serosa, noncollapsing lungs with fluid exudation, enlarged lymph nodes, and progressive pallor and friability of the liver (Bell et al., 2016). Histological lesions consisted of foci of degeneration and cell death in the haired skin, liver, pancreas, adrenal glands, lymph nodes, tongue, esophagus, salivary glands, renal pelvis, small intestine, and large intestine (Bell et al., 2016). In addition to direct cellular injury from viral infection, elevated levels of proinflammatory cytokines, including interferon α, tumor necrosis factor-α (TNF-α), IL-6, IL-8, and IL-10 during peak viral loads and the later stage infections may contribute to damage through a hyperinflammatory response (Sarute and Ross, 2017).

Similar to humans, neurological symptoms have been reported in animal models of SAHF viruses and provide evidence for direct viral infection of the central nervous system. Neonatal mice inoculated intraperitoneally with Tacaribe virus (TCRV) develop seizures, hind limb paralysis, and death within 15 days of inoculation (Ireland et al., 2017). In this mouse model, infection leads to central nervous system inflammation with T cell and monocyte infiltration into the cerebellar parenchyma, apoptosis of astrocytes, neuronal degeneration, and loss of Purkinje cells (Ireland et al., 2017).

SAHF viruses hijack normal cellular mechanisms for their own proliferation; and in doing so, using these as targets for therapeutics is challenging as they are essential for carrying out many normal cellular functions (Brunetti et al., 2018). Viral genomic transcription occurs in the cell and then, using the SK1/S1P cellular protease, the viral proteins are cleaved and processed into virions for budding with the appropriate viral GP coat (Sarute and Ross, 2017). SAHF viruses activate the autophagy pathways, which enhance viral proliferation and spread upon cell apoptosis (Perez Vidakovics et al., 2019). Targeting these pathways for therapeutics is challenging as they are essential for carrying out many normal cellular functions.

As with many viruses, SAHF encodes for genes with immunomodulatory activity to assist with the evasion of detection. SAHF nucleoproteins can block type I interferon production through the inhibition of 2 cellular protein sensors involved with foreign RNA recognition (RIG-I and PACT) (Shao et al., 2018). Additionally, they can modulate the effects of interferon-induced, double-stranded RNA-dependent protein kinase (PKR) activity from an antiviral activity to a proviral state as demonstrated by the augmentation of replication of JUNV and MACV in the presence of PKR (Huang et al., 2017).

Clinical spectrum of infection

Asymptomatic infections with MACV and JUNV have been described in the literature (Weissenbacher et al., 1983; Patterson et al., 2014). Disease, at least for AHF, has been described as milder in children and more severe in pregnant women, with up to a 50%

Figure 1. SAHF disease course.

mortality (Enria et al., 2008; Grant et al., 2012). Less than one-third of patients with SAHF succumb to the illness and approximately 80% of patients will recover within 2 weeks.

Clinical course

Most SAHF cases present with similar clinical manifestations. Infection is 4 times more prevalent among male subjects, who are more likely to work in agriculture, than it is among female subjects. Disease presentation is seasonal and usually reflects harvest seasons for each endemic area. The annual incidence of SAHF, particularly AHF, strongly correlates with the concentration of the rodent reservoir population (Mills et al., 1994). This pattern of disease, related to a specific epidemiological exposure, has been interrupted in Argentina by the introduction of immunization against JUNV in high-risk populations and in Bolivia following the implementation of rodent control measures (Patterson et al., 2014).

After the incubation period, a prodromal phase lasting 1–5 days occurs, which typically involves fever, malaise, myalgia, anorexia, and headaches. By the end of the prodromal phase, patients commonly develop nausea, emesis, and abdominal pain as well as conjunctivitis, gingival bleeding, and dizziness. During the second week of illness, dehydration, hypotension, and confusion are common. It is during this second week of illness that the minority of patients (less than one-third) will develop severe disease with neurological manifestations, including tremors, delirium, ataxia, hypo/areflexia, decreased muscular tone, seizures, and coma; and hemorrhagic manifestations, including petechiae, ecchymosis, gingivorrhagia, hematemesis and melena, hematuria, and metrorrhagia. This phase can lead to multiorgan failure and death [Figure 1]. Most symptomatic patients have the evidence of leukopenia, thrombocytopenia, and proteinuria. Interestingly, patients with VHF may present with respiratory symptoms such as cough, odynophagia, and tonsillar exudates; findings which have not been described for AHF, BrHF, BHF, or CHAPV-HF [Tables 3 and 4].

Ten percent of AHF patients who receive JUNV convalescent plasma as part of their treatment will develop Late Neurologic Syndrome (LNS), particularly those who receive the treatment after 8 days from the onset of illness (Enria et al., 2008; Gomez et al., 2011). Commonly, patients report dizziness, headache, and nausea after recovery. After being symptom-free for a period of time, LNS patients develop fever, cranial nerve palsies, and cerebellar deficits. Almost two-thirds of LNS patients develop tinnitus, blurred vision, and gait ataxia within 7 days and 40% report diplopia (Enria et al., 1985). The most common cranial nerve involved is the Abducens nerve (CN-VI), with involvement described in up to 60% of LNS patients. The most common cerebellar deficits include nystagmus and ataxia in up to 50% of LNS cases. Other deficits, such as hypo or hyperreflexia, extrapyramidal signs, or paresis have been reported in fewer than 10% of LNS patients. Cerebrospinal fluid (CSF) of LNS cases typically demonstrates a lymphocyte-predominant elevated white blood cell (WBC) count, normal glucose and protein, and antibody titers to JUNV higher than those in serum. This CSF finding suggests an immune-mediated mechanism as the causative of LNS; however, the pathophysiology is not well-understood. These symptoms are transient, with most cases that resolve within a few days, but may persist several months (usually less than 4 months) (Enria et al., 1985).

The fatality rate for SAHFs is generally 25%–35%. For AHF, in particular, 80% will survive with noticeable improvement beginning between days 10 and 12 of disease. While only 8 cases of CHAPV-HF have been reported thus far, 4 of those cases resulted in a fatal outcome (Aguilar et al., 2009; Escalera-Antezana et al., 2020). Conversely, patients with AHF who receive treatment with JUNV convalescent plasma, result in a reported mortality of less than 1% (Harrison et al., 1999; Escalera-Antezana et al., 2020).

Table 3
Clinical presentation of South American Hemorrhagic Fevers (SAHF).

Hemorrhagic Fever	Arenavirus	Geographic distribution	Incubation	Early clinical manifestations	Late Clinical manifestations	Mortality
Argentine Hemorrhagic Fever	Junín Virus	Argentina, Buenos Aires, Santa Fe, La Pampa, and Córdoba provinces	6–14 days	Flu-like syndrome. Lack of respiratory symptoms is cardinal	Late Neurological syndrome (LNS)	15%–30% <1% with treatment
Bolivian Hemorrhagic Fever	Machupo Virus	Bolivia, Itenez province	3–16 days	Flu-like syndrome. One-third of cases may progress to progressive neurological and hemorrhagic syndrome	None reported	25%
	Chaparé virus	Bolivia, Cochabamba (small outbreak late 2003, 1 fatality)	3–16 days	Flu-like syndrome Gastrointestinal bleed May progress to ARDS and multiorgan failure.	None reported	60%
Venezuelan Hemorrhagic fever	Guanarito virus	Venezuela, Portuguesa and Barinas state	Up to 19 days	Flu-like syndrome. May present with Upper Respiratory symptoms. May progress to progressive neurological and hemorrhagical syndrome.	None reported	33%
Brazilian Hemorrhagic Fever	Sabiá virus	Brazil, Sao Paulo	6–21 days	Flu-like syndrome, may progress to multiorgan failure	None reported	50%

Table 4
Signs and Symptoms- SAHF.

Common clinical features of SAHF	Argentine HF	Venezuelan HF	Bolivian HF	Brazilian HF[e]
Signs and symptoms				
Fever	97%	92.7%	>90%	100%
Malaise	74%	74.5%	[d]	100%
Headache	58%	58.2%	[d]	100%
Myalgia	54% LBP 64%	31%	[d]	100%
Arthralgia	52%	53%	Not reported	Not reported
Oral enanthem	87%	[a]	[a]	[a]
Odynophagia	Not described	36.5% (Tonsillar exudates 13%)	[a]	33%
Cough	Not described	20%	Not described	Not described
Nausea	45%	13%	[d]	100%
Vomiting	34%	34%	[c]	70%
Diarrhea	27%	27%	[b]	[a]
Abdominal Pain	30%	31%	[c]	[a]
Gingival bleeding	12%	53%	[d]	100%
Dehydration	30%	30%	[b]	33% (leading to multiorgan failure)
Hemorrhagic symptoms (GI tract and GU track)	20– 30% (2nd week)	-Melena: 20% -Hematemesis: 16.4% -Rectal bleeding: 9%	[b](one-third of patients)	-Metrorrhagia 33% -Hematemesis 33%
Seizures	18% (2nd week and poor prognosis)	18.2%	[b]	33%
Neurological symptoms (confusion, tremors, lethargy, and coma)	- 16% Tremors (tongue and hands) - progressive symptoms (poor prognosis)	Approximately one-third	[b](one-third of patients)	Approximately one-third
Physical exam findings				
Petechial rash	60% (common in axilla, soft palate, and gingival margin in 1st week)	16%	[c]	33% (conjunctival petechiae)
Lymphadenopathies	87% (cervical)	24%	[c]	66% (cervical)
Hepatomegaly	Not common	6%	[a]	
Splenomegaly	Not common	2%	[a]	
Conjunctival congestion/periorbital edema	90.3%	15%	[c]	Not described
Laboratory findings				
Thrombocytopenia <100,000/mm^3	100%	100%	100%	66%
Leukopenia <4000/mm^3	87%	85.7%	100%	66%
Proteinuria >1 g/L	42%	Not described	[c]	33%
Other				
Late Neurological Syndrome	10% of cases treated with Junín virus immune plasma	Not described	Not described	Not described
Mortality	15%– 30% (<1% with treatment)	33%	6%– 15%	33%

LBP: low back pain.
[a] literature does not specify the presence or frequency of sign/symptom.
[b] described in cases without the specification of frequency of finding.
[c] described as “often” present without the specification of frequency of finding.
[d] described as present in “most cases” without the specification of frequency of finding.
[e] based on 3 cases, 2 were laboratory-acquired.

The convalescence phase, mostly described for AHF, may last up to 12 weeks and is characterized by fatigue, irritability, memory impairment, dizziness, and hair loss. The convalescent phase for BHF has been described to be up to 2 months and characterized mostly by hair loss, dizziness, and fatigue.

Special patient populations

AHF during pregnancy has been infrequently reported; however, it has been described to have a mortality of near 50% when presenting during the third trimester. Fetal and neonatal deaths as well as congenital malformations have been reported in association with JUNV infection during pregnancy. Most children with AHF appear to have mild disease (Enria et al., 2008; Grant et al., 2012).

SAHF case definition

There is an absence of an internationally accepted SAHF case definition, although some published literature encourages the use of case definitions for AHF and VHF, which aided to propose a case definition for BHF, BrHF, and CHAPV-HF:

- *AHF case definition*: Probable case: an acute febrile illness in a patient with possible exposure, within the previous 3 weeks, to AHF endemic area and to field rodents. Confirmed case: a clinical case as described above, plus a laboratory confirmation of JUNV infection, either by the isolation of the virus or seroconversion (fourfold elevation in titer of the neutralization of antibodies to JUNV between the acute and convalescent phase). It has been proposed that laboratory findings be used to support the case definition, particularly while trying to make decisions regarding the use of convalescent plasma treatment and while awaiting confirmatory testing results. In endemic areas, the combination of thrombocytopenia (defined as a platelet count below 100,000/mm^3) and leukopenia (defined as a WBC count below 4,000/mm^3) has a sensitivity of 100% and a specificity of 71% for AHF (Harrison et al., 1999).
- *VHF case definition*: Probable case: an acute febrile illness in the presence of at least 3 of the following: weakness, headaches, myalgia, odynophagia, vomiting, and/or diarrhea, any kind of hemorrhagic manifestations, leukopenia, and thrombocytopenia. These must be present in a person who lives in or has recently visited a VHF-endemic zone. Confirmed case: the presence of a clinical presentation as described above for a

probable case plus the evidence of GTOV infection through laboratory testing confirming the isolation of the virus or seroconversion (de Manzione et al., 1998).

- *BHF case definition*: Similar to AHF and VHF, this is defined as an acute febrile illness in a patient with possible exposure, within the previous 3 weeks, to a BHF endemic area and to field rodents, or a close contact to a confirmed BHF case. Confirmed case: the presence of a clinical presentation as described for a probable case plus the evidence of MACV infection through laboratory testing confirming the isolation of the virus or seroconversion.
- *CHAPV-HF*: Because of the paucity of cases, there is no agreed-upon case definition. In December 2003 and January 2004, there was a small outbreak of hemorrhagic fever cases in Cochabamba, Bolivia. Information about the outbreak was scant; however, samples from a fatal case pointed to CHAPV, a second arenavirus causing hemorrhagic fever in Bolivia. One case, a previously heathy young farmer, had a clinical course that included fever, arthralgia, myalgia, and headache, which subsequently progressed to multiorgan failure and multiple hemorrhagic signs (Delgado et al., 2008). A publication in early 2020 describes a recent small cluster of 5 patients with hemorrhagic fever and a case fatality rate of 60%, caused by CHAPV, with clinical presentation similar to the earlier described case. The index case was a farmer and all 5 cases presented with fever and gastrointestinal bleed as well as thrombocytopenia. The 3 fatal cases developed ARDS and multiorgan failure. Three of the 5 cases were due to secondary infection among healthcare workers (Escalera-Antezana et al., 2020).
- *BrHF case definition*: Because of the paucity of cases, the lack of host/vector identification, and the yet undefined endemic area as well as the geographic coexistence of other viral hemorrhagic fevers (such as yellow fever and dengue hemorrhagic fever); generating a case definition for BrHF is challenging. Only 4 cases have been reported thus far, 2 wild cases and 2 laboratory-acquired cases (Barry et al., 1995; Ryder and Gandsman, 1995; Gandsman et al., 1997; Saude, 2020). The first wild infection was diagnosed in São Paulo in 1990, in a previously healthy, young, female agricultural engineer, with no field exposure within 21 days of diagnosis (Lisieux et al., 1994). The second wild case, diagnosed in Sao Paulo in January of 2020, was a previously healthy, young, male agricultural worker with recent field exposure (Saude, 2020). A high index of suspicion is necessary in a patient with febrile illness and who develops hemorrhagic features. The inclusion of SBAV infection to the differential diagnosis of a patient with a hemorrhagic fever is fundamental for an early diagnosis.

To diagnose a Viral Hemorrhagic Fever requires a high index of suspicion and a skillfully obtained travel history. Asking oneself "why a patient returning from a specific geographical area, developed a certain symptomatic conundrum in this point of time?" will help keep a high level of alert and prevent staff exposure. Early isolation is important for healthcare professionals and community safety. Because the initial symptoms of viral hemorrhagic fevers are nonspecific, clinicians must carefully consider patients' individual risk factors, such as exposures (leisure and work-related), underlying medical problems, regional and seasonal epidemiology, in conjunction with patient's presentation for early identification and treatment of these patients.

Mortality risk factors

Most persons with ultimately fatal cases of SAHF will develop severe neurological and hemorrhagical manifestations during the second week of the disease. Most patients who will survive the infection will begin clinical improvement during the second week of illness. Risk factors outlined below for fatal outcome due to a SAHF were mostly described for JUNV, MACV, and GTOV infections. There is currently limited information, due to the small number of cases, for CHAPV and SBAV infections prognostic factors. Risk factors for increased mortality due to a SAHF include: (Enria et al., 2008; MacDermott and Ksiazek, 2018).

- Development of hemorrhagic features
- Development of neurological symptoms
- Shock with multiorgan failure
- Sepsis and bacterial superinfection
- Elevated TNF-a, IL-6, IL-8, IL-10, C-GSF, and thrombopoetin levels (Marta et al., 2000)
- Marked thrombocytopenia and leukopenia (Shao et al., 2015)

Diagnostic testing

Similar to other BSL 4 pathogens, access to facilities capable of testing for these viruses may be limited. The use of immunohistochemistry, viral culture, and RT-PCR can be performed to identify the causative agent from samples such as blood or tissue. An extensive review of diagnostic tests for SAHF viruses is beyond the scope of this review. Clinicians in the United States (U.S.) should first contact their state health department regarding a patient under investigation with suspected SAHFs prior to submitting any specimens. If the state health department prefers that specimens go directly to the Centers for Disease Control and Prevention (CDC) for testing, the specimens will be shipped to the Division of High Consequence Pathogens and Pathology (DHCPP), CDC (https://www.cdc.gov/ncezid/dhcpp/index.html [cdc.gov]) within the Viral Special Pathogens Branch (https://www.cdc.gov/ncezid/dhcpp/vspb/index.html [cdc.gov]). Other potential sites for such shipments include the BSL 4 laboratories or the Diagnostics Systems Division at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) – 1-800-USA-RIID. Guidelines for collecting, packing, and shipping of specimens from patients suspected of SAHFs share similar characteristics as those for Ebola virus specimens (https://www.cdc.gov/vhf/ebola/laboratory-personnel/specimens.html) and should adhere to IATA guidelines for category A agents.

Potential treatment or prophylaxis countermeasures

Pre-exposure prophylaxis

Junin vaccines

JUNV is the only SAHF virus for which preventative vaccination is available. Candid #1, a live attenuated vaccine for the prevention of AHF, was developed jointly by the Argentine Ministry of Health and Social Action and the U.S. Army Medical Research Institute of Infectious Diseases. The vaccine became available in 1991 and is only licensed for use in Argentina. The lyophilized vaccine is stable for 30 days when stored between 2 °C and 8 °C and for 9 years when stored between −18 °C and −20 °C (Saavedra et al., 2017). Once reconstituted, the vaccine is stable for 12 h at 2 °C −8 °C (Saavedra et al., 2017).

Vaccination with doses as low as 16 plaque-forming units of Candid #1 provide protection against lethal JUNV challenge in rhesus macaques immunized 3 months prior to challenge (McKee et al., 1992). Vaccine virus is frequently detectable in peripheral blood mononuclear cells from vaccinated monkeys for up to 21 days after immunization although it is only rarely detectable in plasma (McKee et al., 1993). Candid #1 elicits a dose-dependent neutralizing antibody response to JUNV in primates although the role of the neutralizing titer in protection against infection is

unclear (McKee et al., 1992; McKee et al., 1993). Preexisting levels of neutralizing antibodies to JUNV did not correlate with protection against JUNV challenge among marmosets previously infected with a related arenavirus; TCRV, despite prior TCRV infection providing protection against JUNV infection, suggesting protection against JUNV may be at least partially mediated by nonhumoral immunity (Weissenbacher et al., 1982). More than 88% of humans develop neutralizing antibodies to JUNV following Candid #1 vaccination although at lower titers as compared to natural JUNV infection, and most vaccine recipients develop JUNV-specific cellular immune responses (Maiztegui et al., 1998; Enria and Oro, 2002; Ambrosio et al., 2011). Neutralizing antibody titers may persist for up to 10 years following vaccination (Enria and Oro, 2002). The estimated effectiveness of Candid #1 for the prevention of AHF is 95%– 98.1% and for the prevention of any symptomatic JUNV infection is 84% (Maiztegui et al., 1998; Enria and Oro, 2002).

Potential adverse events of Candid #1 vaccination include fever, headache, pharyngitis, retro-orbital pain, myalgia, weakness, nausea, vomiting, dizziness, microscopic hematuria, backache, rash, leukopenia, and thrombocytopenia (Maiztegui et al., 1998; Enria et al., 2010). However, large scale studies have demonstrated that Candid#1 vaccination is well tolerated with 0.1%-1.1% of recipients in large-scale trials that report adverse events, most commonly fever or headache with or without constitutional symptoms (Maiztegui et al., 1998; Enria and Oro, 2002).

Other JUNV vaccines in development include a Venezuelan equine encephalitis virus-based viral replicon vaccine incorporating the GP precursor gene from JUNV, which provided 100% protection against lethal JUNV challenge in guinea pigs after 2 doses (Seregin et al., 2010), a recombinant vaccinia virus vaccine containing the JUNV GP precursor gene, which provided 72% protection in guinea pigs after 2 doses (López et al., 2000), and a tri-segmented live, attenuated MACV vaccine that provided 50% protection against a lethal challenge against the Espindola strain of JUNV in guinea pigs (Zaza et al., 2018).

Currently, Candid #1 vaccine is offered to nonpregnant individuals 15– 65 years of age, who reside in endemic areas in Argentina, including some regions of Buenos Aires, Cordoba, Santa Fe, and La Pampa provinces. Information on how to access Candid #1 vaccine may be found at www.argentina.gob.ar/salud/vacunas/fiebre-hemorragica.

Machupo vaccines

Vaccines against MACV are in development; none are licensed or have been trialed in humans or nonhuman primates. Recombinant MACV vaccines that utilize the GP precursor gene from Candid #1 vaccine yielded some protection in murine models (Koma et al., 2015; Koma et al., 2016). DNA vaccines containing the MACV GP precursor gene delivered in conjunction with electroporation in rabbits elicited neutralizing antibodies to MACV (Golden et al., 2016). Some data suggest that vaccination with attenuated JUNV vaccines, including Candid #1, may provide cross-protection against MACV (Peters et al., 1987; Martinez Peralta et al., 1993; Clark et al., 2018).

Guanarito, Sabiá, and Chaparé vaccines

No licensed vaccine against GTOV, SBAV, or CHAPV exist or have been studied in human or nonhuman primate studies. The inoculation of guinea pigs with an attenuated MACV strain (Car91) yielded partial protection against a lethal GTOV challenge (Golden et al., 2017). Similar to MACV, vaccination with GTOV GP precursor gene DNA delivered with electroporation can elicit GTOV-neutralizing antibodies in rabbits (Golden et al., 2016).

Cross-protective vaccines

Vaccines designed to protect against more than one SAHF are in early development and have not yet entered human or nonhuman primate trials. These include a bivalent virus-like particle vaccine for JUNV and MACV (Carrion et al., 2012) and a cocktail of 14 selected proteins containing CD8+T cell epitopes, to 7NW arenaviruses (Kotturi et al., 2009).

Post-exposure prophylaxis

To our knowledge, the use of antiviral medications, immunomodulatory medications, passive immunization, or active immunization with Candid #1 vaccine as postexposure prophylaxis against disease caused by SAHF viruses in humans has not been reported.

Evidence from animal studies supports a significant potential survival benefit from 2 antiviral medications, ribavirin and favipiravir, administered as postexposure prophylaxis. A 10-day course of ribavirin, initiated on the day of exposure, improved survival from MACV in guinea pigs (Stephen et al., 1980). Prophylaxis with 10 - 28 days of ribavirin decreased mortality in guinea pigs following Pichindé virus (a clade A NW arenavirus) exposure (Lucia et al., 1989; Smee et al., 1993). Postexposure prophylaxis with ribavirin in animal models of JUNV increased survival although some animals receiving prophylaxis developed LNS symptoms (Blejer et al., 1984; Kenyon et al., 1986a; Avila et al., 1987; McKee et al., 1988; Salazar et al., 2012). One guideline suggests the off-label use of oral ribavirin, 500 mg 4 times daily for 7 days, may be considered for postexposure prophylaxis in people with a high-risk exposure to either JUNV or MACV (Bossi et al., 2004).

Postexposure prophylaxis with favipiravir improved survival in guinea pigs exposed to JUNV, even when initiated up to 5 days after exposure; although the oral administration of favipiravir was significantly less effective than intraperitoneal administration (Gowen et al., 2013; Gowen et al., 2017). The administration of favipiravir or a related pyrazine compound, T-1106, improved survival in mice and hamsters when administered following exposure to the Pichinde virus (Gowen et al., 2007; Gowen et al., 2010). No specific guidelines exist for postexposure dosing of favipiravir in humans for the prevention of SAHF, and favipiravir is not licensed in many countries, including the U.S. where an emergency investigational drug approval would be required for administration (Toyama Chemical Company Limited). Favipiravir is licensed for the treatment of influenza in Japan. A 10-day postexposure regimen of favipiravir for postexposure prophylaxis against Ebola virus, which consists of 3 loading doses (2400 mg, 2400 mg, and 1200 mg orally every 8 h) on day 1 followed by 1200 mg orally twice daily, was well tolerated in a small case series (Jacobs et al., 2015).

Although passive immunization against JUNV infection demonstrates clear treatment benefits, the risks and benefits of antibody transfer as postexposure prophylaxis as compared to antiviral medications are unclear. Passive antibody administration improves survival against AHF and BHF in animal models; however, some animals developed LNS symptoms associated with the presence of virus in the central nervous system, which indicates that antibody transfer does not provide protection against the development of neurological infection (Eddy et al., 1975; Kenyon et al., 1986b; Golden et al., 2016).

There are some data to support the use of immunomodulatory medications for postexposure prophylaxis for SAHF viruses. Administration of interferon-α up to 24 h after Pichindé virus exposure provided significant protection against mortality in guinea pigs and hamsters (Gowen et al., 2005; Gowen et al., 2011). A synergistic beneficial survival effect was observed when prophylaxis with interferon-α was combined with ribavirin and initiated early after exposure to Pichindé virus in guinea pigs (Gowen et al., 2006). Two studies demonstrated a survival benefit

following the postexposure administration of synthetic oligodeoxynucleotides that contain methylated CpG motifs, immunostimulatory molecules, which mimic bacterial DNA used in some adjuvanted vaccines, with or without concurrent anti-TNF-α antibodies in neonatal mice when initiated up to 3 days after exposure to TCRV, a clade B NW arenavirus associated with nonfatal, febrile illness in humans (Pedras-Vasconcelos et al., 2006; Pedras-Vasconcelos et al., 2008).

Treatment

Supportive therapy continues to be the mainstay of treatment for SAHF infections; however, there are a few evidence-based therapeutic interventions that could be considered.

Immune serum

Historically, several viruses were treated with immune sera, and immune plasma has been used for the treatment of JUNV infection nearly since its discovery in 1958. In 1979, a double blind placebo-controlled study in patients with suspected JUNV infection and less than 8 days of clinical symptoms found that treatment with 500 ml of immune plasma resulted in a mortality rate of 1.1% when compared with 16.5% in the untreated control group (Maiztegui et al., 1979). When given to patients who had symptoms for more than 8 days, this treatment did not show any benefit (Enria et al., 2008). Given recent improvements in the control of exposure and mass vaccination, the prevalence of JUNV infection has decreased. As a result, decreasing quantities of convalescent serum are available due to decreases in the available donor pool. Clinicians interested in obtaining convalescent plasma against AHF shouldbe obtained by contacting the Instituto Nacional de Enfermedades Virales Humanas (INEVH) in Perganmino, Buenos Aires, Argentina (http://www.anlis.gov.ar/inevh/).

For MACV, passive immunization improves outcomes in rhesus macaques. Monkeys experimentally infected with MACV who were given anti-MACV human immunoglobulin 4 h after virus inoculation initially survived; however, monkeys who received the highest dose of immunoglobulin further developed LNS that results in death in 3 out of the 4 infected monkeys (Eddy et al., 1975). To our knowledge, there have not been documented clinical trials of immunoglobulin transfer in human MACV patients.

There are some risks and limitations to the use of this treatment. Patients treated with convalescent sera are at a risk to develop LNS, which has been observed in NHPs and in humans (Enria et al., 1984; Enria et al., 1985; Kenyon et al., 1986b; Avila et al., 1987). While the mechanism for this is not clear, it is suggested that it may be related to high viral titers in the brain that treatment with convalescent serum is unable to prevent. It is unclear if patients who develop LNS have more severe disease at baseline. Additionally, the use of convalescent sera may be difficult in cases of exposure in nonendemic settings where convalescent serum may not be available or in countries that may have ethical or logistical restrictions on treatment. These limitations place an increased importance on the development and use of other antiviral alternatives for treatment of SAHF.

Ribavirin

Ribavirin is a guanosine analog shown to have activity against several hemorrhagic fever viruses (Huggins 1989; Huggins et al., 1991). Animal studies have shown the activity of ribavirin against several arenaviruses (Stephen et al., 1980; Smee et al., 1993). Four rhesus macaques infected with JUNV received ribavirin on day 6 of disease. Of these, 1 died early. The other 3 macaques survived the initial phase of clinical illness; however, they all then developed severe neurological signs and 2 of them died (McKee et al., 1988). In an experimental model with guinea pigs infected with JUNV, animals treated with ribavirin had on average 6.7 more days to death when compared with the control group. Ribavirin treatment also delayed the presentation of severity of symptoms (Salazar et al., 2012). In a double blind trial of ribavirin vs placebo in confirmed JUNV infection, 1 of 8 patients in the ribavirin group died as compared to 4 of 10 patients in the placebo group (Enria and Maiztegui, 1994).

In a case series of 3 MACV patients, 2 patients with laboratory-confirmed MACV recovered with ribavirin, while a third patient with confirmed infection died (Kilgore et al., 1997). One patient who acquired SBAV through a laboratory contact was treated with ribavirin and survived (Barry et al., 1995).

The main limitations of ribavirin include its well-known side effect of anemia and teratogenicity during pregnancy. Ribavirin analogs have been studied, which may allow a reduction in ribavirin dose and side effects (Contin et al., 2019). Ribavirin is not licensed in the U.S. for the treatment of SAHF.

Favipiravir

Favipiravir is a selective inhibitor of viral RNA polymerase and is active against several RNA viruses (Furuta et al., 2017; De Clercq, 2019). Favipiravir was used to treat patients infected with Ebola during the West Africa outbreak, though its efficacy in this scenario was difficult to ascertain due to conditions of the study (Sissoko et al., 2016). In cell cultures, favipiravir has been found to be active against MACV and GTOV through the disruption of viral replication (Mendenhall et al., 2011; Furuta et al., 2017). In a study of guinea pigs infected with JUNV, those treated with favipiravir survived longer than those treated with placebo and had lower viral titers (Gowen et al., 2013). Favipiravir is not currently licensed in the United States; however, it is licensed in Japan for the treatment of influenza.

The addition of low-dose ribavirin synergistically potentiates the activity of favipiravir against JUNV in guinea pigs (Westover et al., 2016). In a study of 2 patients with Lassa fever, favipiravir and ribavirin were used as a combination therapy, which resulted in the survival of both patients, but patients had elevated transaminases and nausea, which may have been due to medications (Raabe et al., 2017). Favipiravir should be used with caution in pregnant women due to potential teratogenicity and embryotoxicity (Nagata et al., 2015).

Monoclonal antibody

Another potential therapeutic strategy includes monoclonal antibodies. In an *in vitro* study, Helguera et al identified an anti-hTfR1 (human transferrin receptor 1) antibody and showed that it inhibited the entry of arenaviruses (Helguera et al., 2012). There is some evidence of the potential neutralization of JUNV by antibodies against nucleoprotein (Linero et al., 2018) and GP 1 receptors, to which strong binding was identified in one study of 5 monoclonal antibodies, which effectively neutralized JUNV (Pan et al., 2018). A recent study identified 5 monoclonal antibodies found to have neutralization activity *in vitro* against MACV, 3 significantly lowered viral loads in the spleen *in vivo* in a murine challenge model (Amanat et al., 2020). The efficacy of monoclonal antibodies against SAHF viruses in human or NHPs has not yet been determined. Monoclonal antibodies against SAHF are not yet commercially available although the development of monoclonal antibodies against JUNV is being pursued by Mapp Biopharmaceutical Inc.

Other therapies

Tripartite motif proteins inhibit SAHF arenavirus entry into cells and limit phagocytosis of apoptotic cells (Sarute et al., 2019). Leflunomide, an immunomodulatory agent used for rheumatoid arthritis, has been shown to inhibit the formation of the

nucleocapsid tegument in JUNV. In one study that looked at the effects of the active metabolite of leflunomide (A771726) on active cell lines, the authors found the inhibition of viral RNA synthesis in treated infected cells (Sepulveda et al., 2018).

Infection prevention and control recommendations

Patients infected with SAHF virus should optimally be managed in a biocontainment unit (Frank et al., 2020; Smith et al., 2006). The risk of secondary person-to-person transmission may vary depending on the virus, however, in the setting of incomplete knowledge of the risks of secondary transmission for all SAHF viruses and the potential severe consequences of exposure, (Kilgore et al., 1995) general guidelines for viral hemorrhagic fever infection control should be implemented. These include isolating the patient in a negative-pressure, single-patient room containing a private bathroom and the restriction of room access to those with proper authority wearing appropriate personal protective equipment. Laboratory studies demonstrate the potential for airborne transmission of arenaviruses associated with causing SAHF (Peters et al., 1987). Contact, droplet, and airborne precautions should be implemented and aerosol-generating procedures should be avoided if possible. The use of sharps should be minimized with proper sharps disposal facilities available within the patient room. Frequent hand hygiene should be performed. Exposure and evaluation management plans should be developed to provide appropriate care, diagnostic testing, and treatment for any employees who experience a potential exposure. Additional guidance on the infection prevention and control measures for patients under investigation for suspected viral hemorrhagic fevers may be found at https://www.cdc.gov/vhf/ebola/clinicians/evd/infection-control.html.

On a local and regional level, community-wide rodent control is important for the prevention and control of SAHF outbreaks (Mackenzie et al., 1967; Kilgore et al., 1995). Candid #1 vaccination should be considered for the prevention of AHF in people residing in endemic regions, people visiting endemic regions with a risk factor for disease exposure, such as engaging in agricultural work, and people in occupations that place them at a high risk of exposure, such as laboratory workers handling JUNV or rodent control workers in endemic regions. Vaccination with Candid #1 vaccine is only currently available in Argentina and would require an investigational new drug approval for use in the United States.

Summary and recommendations

Supportive care continues to be the pillar stone of therapy for viral hemorrhagic fevers. Adequate resuscitation of volume loss, close monitoring of vital signs, electrolyte and acid base monitoring, transfusions when required, and support of organ damage are vital.

There are data in animal and human studies to support the use of ribavirin as an antiviral. The suggested dose in adults is: loading dose is 34 mg/kg x1, followed by 17 mg/kg q6h for 4 days, and followed by 8 mg/kg q8h for 6 days (Enria et al., 2008). When using ribavirin, it is important to monitor for the development of hemolytic anemia, which is a well-known side effect. A similar syndrome to late neurological syndrome has been described in patients treated with ribavirin. Combination therapy with ribavirin (16 mg/kg IV every 6 h) and favipiravir (2000 mg orally once, followed by 1000 mg every 12 h) has been used successfully in Lassa fever (Raabe et al., 2017) and is reasonable to use in SAHF. Recently, a woman who presented in Belgium with Lassa fever was treated with the combination therapy, though ribavirin was discontinued due to hemolytic anemia (https://wwwnc.cdc.gov/eid/article/26/7/20-0275_article).

Convalescent serum continues to be the most studied and documented treatment in humans, and its use should be considered when treatment is available. The main concern with this therapy is the lack of availability, particularly given the recent decrease in the number of infections that deplete the potential donor pool. This therapy is effective when used within the first 8 days of symptoms. Close monitoring should be considered for the development of late neurological symptom with this therapy.

Vaccine development is promising in the prevention of JUNV, and possibly in other SAHF. Vaccines have been widely used in Argentina, though due to the decrease in numbers they are no longer provided by the government. Given the rarity of infection, clinicians may be unlikely to suspect SAHF viral infections, which may lead to delays in diagnosis and treatment that lead to increases in mortality.

Finally, the ongoing development of new antiviral therapies may prove to be promising in the treatment of SAHF in the future. An emphasis will probably be placed on alternatives to ribavirin, due to the side effects associated with ribavirin, or ribavirin combination therapy, which can decrease the amount of ribavirin required to be effective. New treatments such as single-strand RNA therapy and several monoclonal antibodies are under study.

We will include treatment options in a table at www.netec.org, which will be updated periodically.

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Ethical approval

The work described herein was solely a review of the literature and as such did not have a requirement for Institutional Review Board or Animal Use Committee approvals.

Appendix A

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.02.046.

References

Aguilar PV, Camargo W, Vargas J, Guevara C, Roca Y, Felices V, et al. Reemergence of Bolivian hemorrhagic fever, 2007-2008. Emerg Infect Dis 2009;15(9):1526–8.

Amanat F, Duehr J, Huang C, Paessler S, Tan GS, Krammer F. Monoclonal antibodies with neutralizing activity and Fc-effector functions against the Machupo virus glycoprotein. J Virol 2020;94(5)e01741-19.

Ambrosio A, Saavedra M, Mariani M, Gamboa G, Maiza A. Argentine hemorrhagic fever vaccines. Hum Vaccin 2011;7(6):694–700.

Avila MM, Sarnoilovich SR, Laguens RP, Merani MS, Weissenbacher MC. Protection of Junín virus-infected marmosets by passive administration of immune serum: association with late neurologic signs. J Med Virol 1987;21(1):67–74.

Barry M, Russi M, Armstrong L, Geller D, Tesh R, Dembry L, et al. Brief report: treatment of a laboratory-acquired Sabia virus infection. N Engl J Med 1995;333(5):294–6.

Bell TM, Bunton TE, Shaia CI, Raymond JW, Honnold SP, Donnelly GC, et al. Pathogenesis of Bolivian hemorrhagic fever in Guinea pigs. Vet Pathol 2016;53(1):190–9.

Blejer JL, Galassi NV, Saavedra VM, Nejamkis MR. Protection conferred against Junin virus infection in rats. Intervirology 1984;21(3):174–7.

Bossi P, Tegnell A, Baka A, van Loock F, Hendriks J, Werner A, et al. Bichat guidelines for the clinical management of haemorrhagic fever viruses and bioterrorism-related haemorrhagic fever viruses. Euro Surveill 2004;9(12):29–30.

Briggiler A, Enria D, Feuillade MR, Maiztegui J. Contagio interhumano e infeccion inaparente por virusJunin in matrimonios del area endemica de fiebre hemorragica Argentina. Medicina (Buenos Aires) 1987;47:565.

Brunetti JE, Foscaldi S, Quintana VM, Scolaro LA, Lopez N, Castilla V. Role of the ERK1/2 signaling pathway in the replication of Junin and Tacaribe viruses. Viruses 2018;10(4).

Carrion Jr R, Bredenbeek P, Jiang X, Tretyakova I, Pushko P, Lukashevich IS. Vaccine platforms to control arenaviral hemorrhagic fevers. J Vaccines Vaccination 2012;3(7)1000160.

Clark LE, Mahmutovic S, Raymond DD, Dilanyan T, Koma T, Manning JT, et al. Vaccine-elicited receptor-binding site antibodies neutralize two new world hemorrhagic fever arenaviruses. Nat Commun 2018;9(1) 1884–1884.

Coffin JM. Virions at the gates: receptors and the host-virus arms race. PLoS Biol 2013;11(5)e1001574.

Contin M, Sepulveda C, Fascio M, Stortz CA, Damonte EB, D'Accorso NB. Modified ribavirin analogues as antiviral agents against Junin virus. Bioorg Med Chem Lett 2019;29(4):556–9.

De Clercq E. New nucleoside analogues for the treatment of hemorrhagic fever virus infections. Chem Asian J 2019;14(22):3962–8.

de Manzione N, Salas RA, Paredes H, Godoy O, Rojas L, Araoz F, et al. Venezuelan hemorrhagic fever: clinical and epidemiological studies of 165 cases. Clin Infect Dis 1998;26(2):308–13.

Delgado S, Erickson BR, Agudo R, Blair PJ, Vallejo E, Albarino CG, et al. "Chapare virus, a newly discovered arenavirus isolated from a fatal hemorrhagic fever case in Bolivia. PLoS Pathog 2008;4(4)e1000047.

Eddy GA, Wagner FS, Scott SK, Mahlandt BJ. Protection of monkeys against Machupo virus by the passive administration of Bolivian haemorrhagic fever immunoglobulin (human origin). Bull World Health Organ 1975;52(4–6):723–7.

Enría DA, Mills JN, Bausch D, Shieh WJ, Peters CJ. Tropical infectious diseases: principles, pathogens, and practice. . p. 449–61 CHAPTER 68.

Enria DA, Ambrosio AM, Briggiler AM, Feuillade MR, Crivelli E, V. Study Group on Argentine Hemorrhagic Fever. Candid#1 vaccine against Argentine hemorrhagic fever produced in Argentina. Immunogenicity and safety. Medicina (B Aires) 2010;70(3):215–22.

Enria DA, Briggiler AM, Fernandez NJ, Levis SC, Maiztegui JI. Importance of dose of neutralising antibodies in treatment of Argentine haemorrhagic fever with immune plasma. Lancet 1984;2(8397):255–6.

Enria DA, Briggiler AM, Sanchez Z. Treatment of Argentine hemorrhagic fever. Antiviral Res 2008;78(1):132–9.

Enria DA, de Damilano AJ, Briggiler AM, Ambrosio AM, Fernandez NJ, Feuillade MR, et al. Late neurologic syndrome in patients with Argentinian hemorrhagic fever treated with immune plasma. Medicina (B Aires) 1985;45(6):615–20.

Enria DA, Maiztegui JI. Antiviral treatment of Argentine hemorrhagic fever. Antiviral Res 1994;23(1):23–31.

Enria DA, Oro JGB. In: Oldstone MBA, editor. Junin virus vaccines. Arenaviruses II: the molecular pathogenesis of Arenavirus infections. Springer Berlin Heidelberg: Berlin, Heidelberg; 2002. p. 239–61.

Escalera-Antezana JP, Rodriguez-Villena OJ, Arancibia-Alba AW, Alvarado-Arnez LE, Bonilla-Aldana DK, Rodriguez-Morales AJ. Clinical features of fatal cases of Chapare virus hemorrhagic fever originating from rural La Paz, Bolivia, 2019: a cluster analysis. Travel Med Infect Dis 2020;101589.

Feuillade MR, E.D. Análisis de la utilidad de la vacuna Candid 1 en la prevención de la Fiebre Hemorrágica Argentina en niños. Revista Panamericana Salud Pública 2005;18:100–6.

Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci 2017;93(7):449–63.

Gandsman EJ, Aaslestad HG, Ouimet TC, Rupp WD. Sabia virus incident at Yale University. Am Ind Hyg Assoc J 1997;58(1):51–3.

Golden JW, Beitzel B, Ladner JT, Mucker EM, Kwilas SA, Palacios G, et al. An attenuated Machupo virus with a disrupted L-segment intergenic region protects guinea pigs against lethal Guanarito virus infection. Sci Rep 2017;7(1)4679–4679.

Golden JW, Maes P, Kwilas SA, Ballantyne J, Hooper JW. Glycoprotein-specific antibodies produced by DNA vaccination protect Guinea pigs from Lethal Argentine and Venezuelan Hemorrhagic Fever. J Virol 2016;90(7):3515–29.

Gomez RM, Jaquenod de Giusti C, Sanchez Vallduvi MM, Frik J, Ferrer MF, Schattner M. Junin virus. A XXI century update. Microbes Infect 2011;13(4):303–11.

Gowen BB, Barnard DL, Smee DF, Wong M-H, Pace AM, Jung K-H, et al. Interferon alfacon-1 protects hamsters from lethal pichinde virus infection. Antimicrob Agents Chemother 2005;49(6):2378–86.

Gowen BB, Ennis J, Russell A, Sefing EJ, Wong M-H, Turner J. Use of recombinant adenovirus vectored consensus IFN-α to avert severe arenavirus infection. PLoS One 2011;6(10) e26072–e26072.

Gowen BB, Juelich TL, Sefing EJ, Brasel T, Smith JK, Zhang L, et al. Favipiravir (T-705) inhibits Junín virus infection and reduces mortality in a guinea pig model of Argentine hemorrhagic fever. PLoS Negl Trop Dis 2013;7(12) e2614–e2614.

Gowen BB, Smee DF, Wong M-H, Pace AM, Jung K-H, Bailey KW, et al. Combinatorial ribavirin and interferon alfacon-1 therapy of acute Arenaviral disease in Hamsters. Antiviral Chem Chemother 2006;17(4):175–83.

Gowen BB, Westover JB, Sefing EJ, Van Wettere AJ, Bailey KW, Wandersee L, et al. Enhanced protection against experimental Junin virus infection through the use of a modified favipiravir loading dose strategy. Antiviral Res 2017;145:131–5.

Gowen BB, Wong M-H, Jung K-H, Sanders AB, Mendenhall M, Bailey KW, et al. In vitro and in vivo activities of T-705 against arenavirus and bunyavirus infections. Antimicrob Agents Chemother 2007;51(9):3168–76.

Gowen BB, Wong M-H, Jung K-H, Smee DF, Morrey JD, Furuta Y. Efficacy of favipiravir (T-705) and T-1106 pyrazine derivatives in phlebovirus disease models. Antiviral Res 2010;86(2):121–7.

Grant A, Seregin A, Huang C, Kolokoltsova O, Brasier A, Peters C, et al. Junin virus pathogenesis and virus replication. Viruses 2012;4(10):2317–39.

Harrison LH, Halsey NA, McKee Jr. KT, Peters CJ, Barrera Oro JG, Briggiler AM, et al. Clinical case definitions for Argentine hemorrhagic fever. Clin Infect Dis 1999;28(5):1091–4.

Helguera G, Jemielity S, Abraham J, Cordo SM, Martinez MG, Rodríguez JA, et al. An antibody recognizing the apical domain of human transferrin receptor 1 efficiently inhibits the entry of all new world hemorrhagic fever arenaviruses. J Virol 2012;86:4024–8.

Huang C, Kolokoltsova OA, Mateer EJ, Koma T, Paessler S. Highly pathogenic new world arenavirus infection activates the pattern recognition receptor protein kinase R without attenuating virus replication in human cells. J Virol 2017;91(20).

Huggins JW. Prospects for treatment of viral hemorrhagic fevers with ribavirin, a broad-spectrum antiviral drug. Rev Infect Dis 1989;11(Suppl 4):S750–761.

Huggins JW, Hsiang CM, Cosgriff TM, Guang MY, Smith JI, Wu ZO, et al. Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. J Infect Dis 1991;164(6):1119–27.

Ireland DD, Tami C, Pedras-Vasconcelos J, Verthelyi D. CD4 and CD8 T cells mediate distinct lethal meningoencephalitis in mice challenged with Tacaribe arenavirus. Cell Mol Immunol 2017;14(1):90–107.

Jacobs M, Bhagani AE, Buchanan S, Cropley R, Hopkins I, Lester S, et al. Post-exposure prophylaxis against Ebola virus disease with experimental antiviral agents: a case-series of health-care workers. Lancet Infect Dis 2015;15:1300–4.

Kenyon RH, Canonico PG, Green DE, Peters CJ. Effect of ribavirin and tributylribavirin on argentine hemorrhagic fever (Junin virus) in guinea pigs. Antimicrob Agents Chemother 1986a;29(3):521–3.

Kenyon RH, Green DE, Eddy GA, Peters CJ. Treatment of junin virus-infected guinea pigs with immune serum: development of late neurological disease. J Med Virol 1986b;20(3):207–18.

Kilgore PE, Ksiazek TG, Rollin PE, Mills JN, Villagra MR, Montenegro MJ, et al. Treatment of Bolivian hemorrhagic fever with intravenous ribavirin. Clin Infect Dis 1997;24(4):718–22.
Kilgore PE, Peters CJ, Mills JN, Rollin PE, Armstrong L, Khan AS, et al. Prospects for the control of Bolivian hemorrhagic fever. Emerg Infect Dis 1995;1(3):97–100.
Koma T, Huang C, Aronson JF, Walker AG, Miller M, Smith JN, et al. The ectodomain of glycoprotein from the candid#1 vaccine strain of Junin virus rendered Machupo virus partially attenuated in mice lacking IFN-αβ/γ receptor. PLoS Negl Trop Dis 2016;10(8) e0004969–e0004969.
Koma T, Patterson M, Huang C, Seregin AV, Maharaj PD, Miller M, et al. Machupo virus expressing GPC of the Candid#1 vaccine strain of Junin virus is highly attenuated and immunogenic. J Virol 2015;90(3):1290–7.
Kotturi MF, Botten J, Sidney J, Bui H-H, Giancola L, Maybeno M, et al. A multivalent and cross-protective vaccine strategy against arenaviruses associated with human disease. PLoS Pathogens 2009;5(12) e1000695–e1000695.
Linero F, Sepulveda C, Christopoulou I, Hulpiau P, Scolaro L, Saelens X. Neutralization of Junin virus by single domain antibodies targeted against the nucleoprotein. Sci Rep 2018;8(1):11451.
Lisieux T, Coimbra M, Nassar ES, Burattini MN, de Souza LT, Ferreira I, et al. New arenavirus isolated in Brazil. Lancet 1994;343(8894):391–2.
López N, Scolaro L, Rossi Carlos, Jácamo R, Candurra N, Pujol C, et al. Homologous and heterologous glycoproteins induce protection against Junin virus challenge in guinea pigs. J Gen Virol 2000;81(5):1273–81.
Lucia HL, Coppenhaver DH, Baron S. Arenavirus infection in the guinea pig model: antiviral therapy with recombinant interferon-alpha, the immunomodulator CL246,738 and ribavirin. Antiviral Res 1989;12(5–6):279–92.
MacDermott N, Ksiazek TG. South American Hemorrhagic Fevers. BMJ Best Pract 2018; Retrieved August 12th, 2019, from https://bestpractice.bmj.com/topics/en-gb/1612. May 2018.
Mackenzie RB, Kuns ML, Webb PA. Possibilities for the control of hemorrhagic fevers in Latin America. Bol Oficina Sanit Panam 1967;62(6):523–30.
Maiztegui JI, Fernandez NJ, de Damilano AJ. Efficacy of immune plasma in treatment of Argentine haemorrhagic fever and association between treatment and a late neurological syndrome. Lancet 1979;2(8154):1216–7.
Maiztegui JI, McKee Jr. KT, Oro JGB, Harrison LH, Gibbs PH, Feuillade MR, et al. Protective efficacy of a live attenuated vaccine against Argentine hemorrhagic fever. J Infect Dis 1998;177(2):277–83.
Frank Maria G, Croyle Caroline, Beitscher Adam, Price Connie. The role of hospitalists in biocontainment units: a perspective. J Hospital Med 2020;15(6):375–7.
Marta RF, Enria D, Molinas FC. Relationship between hematopoietic growth factors levels and hematological parameters in Argentine hemorrhagic fever. Am J Hematol 2000;64(1):1–6.
Martinez Peralta L, Coto CE, Weissenbacher MC. The tacaribe complex: The close relationship between a pathogenic (Junin) and a nonpathogenic (Tacaribe) Arenavirus. In: Salvato MS, editor. . The arenaviridae. New York: Plenum Press; 1993. p. 281–96.
McKee JKT, Barrera Oro JG, Kuehne AI, Spisso JA, Mahlandt BG. Candid No. 1 Argentine hemorrhagic fever vaccine protects against Lethal Junin virus challenge in Rhesus Macaques. Intervirology 1992;34(3):154–63.
McKee Jr KT, Huggins JW, Trahan CJ, Mahlandt BG. Ribavirin prophylaxis and therapy for experimental argentine hemorrhagic fever. Antimicrob Agents Chemother 1988;32(9):1304–9.
McKee Jr KT, Oro JG, Kuehne AI, Spisso JA, Mahlandt BG. Safety and immunogenicity of a live-attenuated Junin (Argentine hemorrhagic fever) vaccine in rhesus macaques. Am J Trop Med Hyg 1993;48(3):403–11.
Mendenhall M, Russell A, Juelich T, Messina EL, Smee DF, Freiberg AN, et al. T-705 (favipiravir) inhibition of arenavirus replication in cell culture. Antimicrob Agents Chemother 2011;55(2):782–7.
Mills JN, Ellis BA, Childs JE, McKee Jr KT, Maiztegui JI, Peters CJ, et al. Prevalence of infection with Junin virus in rodent populations in the epidemic area of Argentine hemorrhagic fever. Am J Trop Med Hyg 1994;51(5):554–62.
Nagata T, Lefor Alan K, Hasegawa M, Ishii M. Favipiravir: a new medication for the Ebola virus disease pandemic. Disaster Med Public Health Preparedness 2015;9(1):79–81.
Pan X, Wu Y, Wang W, Zhang L, Xiao G. Novel neutralizing monoclonal antibodies against Junin virus. Antiviral Res 2018;156:21–8.
Patterson M, Grant A, Paessler S. Epidemiology and pathogenesis of Bolivian hemorrhagic fever. Curr Opin Virol 2014;5:82–90.
Pedras-Vasconcelos JA, Goucher D, Puig M, Tonelli LH, Wang V, Ito S, et al. CpG oligodeoxynucleotides protect newborn mice from a lethal challenge with the Neurotropic Tacaribe Arenavirus. J Immunol 2006;176(8):4940–9.
Pedras-Vasconcelos JA, Puig M, Sauder C, Wolbert C, Ovanesov M, Goucher D, et al. Immunotherapy with CpG oligonucleotides and antibodies to TNF-α rescues neonatal mice from lethal Arenavirus-Induced Meningoencephalitis. J Immunol 2008;180(12):8231–40.
Perez Vidakovics MLA, Ure AE, Arrias PN, Romanowski V, Gomez RM. Junin virus induces autophagy in human A549 cells. PLoS One 2019;14(6)e0218730.
Peters CJ, Jahrling PB, Liu CT, Kenyon RH, McKee Jr. KT, Barrera Oro JG. Experimental studies of arenaviral hemorrhagic fevers. Curr Top Microbiol Immunol 1987;134:5–68.
Raabe VN, Kann G, Ribner BS, Morales A, Varkey JB, Mehta AK, et al. Favipiravir and ribavirin treatment of epidemiologically linked cases of lassa fever. Clin Infect Dis 2017;65(5):855–9.
Ryder RW, Gandsman EJ. Laboratory-acquired Sabia virus infection. N Engl J Med 1995;333(25):1716.
Saavedra MDC, Riera LM, Bottale AJ, Mariani MA, Maiza AS, Ambrosio AM. Stability of Candid#1 vaccine to prevent Argentine Hemorrhagic Fever. Medicina (B Aires) 2017;77(5):353–7.
Salas R, de Manzione N, Tesh RB, Rico-Hesse R, Shope RE, Betancourt A, et al. Venezuelan haemorrhagic fever. Lancet 1991;338(8774):1033–6.
Salazar M, Yun NE, Poussard AL, Smith JN, Smith JK, Kolokoltsova OA, et al. Effect of ribavirin on junin virus infection in guinea pigs. Zoonoses Public Health 2012;59(4):278–85.
Sarute N, Ibrahim N, Medegan Fagla B, Lavanya M, Cuevas C, Stavrou S, et al. TRIM2, a novel member of the antiviral family, limits New World arenavirus entry. PLoS Biol 2019;17(2)e3000137.
Sarute N, Ross SR. New world arenavirus biology. Annu Rev Virol 2017;4(1):141–58.
Ministerio da Saude. Secretaria de Vigilancia em Saude. identificacao de um caso de febre hemorragica brasileira no estado de sao Paulo, janeiro de 2020. Boletim Epidemiol 2020;51(03):8.
Sepulveda CS, Garcia CC, Damonte EB. Antiviral activity of A771726, the active metabolite of leflunomide, against Junin virus. J Med Virol 2018;90(5):819–27.
Seregin AV, Yun NE, Poussard AL, Peng BH, Smith JK, Smith JN, et al. TC83 replicon vectored vaccine provides protection against Junin virus in guinea pigs. Vaccine 2010;28(30):4713–8.
Shao J, Huang Q, Liu X, Di D, Liang Y, Ly H. Arenaviral nucleoproteins suppress PACT-induced Augmentation of RIG-I function to inhibit type I interferon production. J Virol 2018;92(13).
Shao J, Liang Y, Ly H. Human hemorrhagic fever causing arenaviruses: molecular mechanisms contributing to virus virulence and disease pathogenesis. Pathogens 2015;4(2):283–306.
Sissoko D, Laouenan C, Folkesson E, M'Lebing AB, Beavogui AH, Baize S, et al. Experimental treatment with favipiravir for Ebola virus disease (the JIKI Trial): a historically controlled, single-arm proof-of-concept trial in guinea. PLoS Med 2016;13(3)e1001967.
Smee DF, Gilbert J, Leonhardt JA, Barnett BB, Huggins JH, Sidwell RW. Treatment of lethal Pichinde virus infections in weanling LVG/Lak hamsters with ribavirin, ribamidine, selenazofurin, and ampligen. Antiviral Res 1993;20(1):57–70.
Smith PW, Anderson Arthur O, Christopher GW, Cieslak TJ, Devreede GJ, Fosdick GA, et al. Designing a biocontainment unit to care for patients with serious communicable diseases: a consensus statement. Biosecur Bioterror 2006;4(4):351–65.
Stephen EL, Jones Dennis E, Peters CJ, Eddya GA, Loizeaux PS, Jahrling PB. In: Smith KW, R.A, editors. Ribavirin treatment of toga-, arena-, and bunyavirus infections in subhuman primates and other laboratory animal species. Ribavirin – a broad spectrum antiviral agent. New York: Academic Press Inc.; 1980. p. 169–83.
Viruses ICoTo. ICTV virus taxonomy, Genus: mammarenavirus. ICTV Online Report. 10th report. 2018.
Weissenbacher MC, Coto CE, Calello MA, Rondinone SN, Damonte EB, Frigerio MJ. Cross-protection in nonhuman primates against Argentine hemorrhagic fever. Infect Immun 1982;35(2):425–30.
Weissenbacher MC, Sabattini MS, Avila MM, Sangiorgio PM, de Sensi MR, Contigiani MS, et al. Junin virus activity in two rural populations of the Argentine hemorrhagic fever (AHF) endemic area. J Med Virol 1983;12(4):273–80.
Westover JB, Sefing EJ, Bailey KW, Van Wettere AJ, Jung KH, Dagley A, et al. Low-dose ribavirin potentiates the antiviral activity of favipiravir against hemorrhagic fever viruses. Antiviral Res 2016;126:62–8.
Zaza AD, Herbreteau CH, Peyrefitte CN. Description and characterization of a novel live-attenuated tri-segmented Machupo virus in Guinea pigs. Virol J 2018;15(1)99-99.