



Unveiling the mysteries of the novel Argentine arenavirus

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Abstract : Arenaviruses, with their distinctive sandy-like appearance under the microscope, have long fascinated researchers due to their pleomorphic shapes and varying diameters spanning from 50 to 300 nm, originating from the Latin term "arena," meaning "sand." Among the approximately 30 known arenaviruses, over a third possess the capability to infect humans, with eight identified as causative agents of diseases ranging from mild illnesses to lethal hemorrhagic fevers, including Junin virus (JUNV), Machupo virus (MACV), Guanarito virus (GTOV), Sabia virus (SABV), and Lassa virus (LASV), linked to severe outbreaks in Argentina, Bolivia, Venezuela, Brazil, and West Africa, respectively. The rich history of Argentine hemorrhagic fever (AHF) intertwines with JUNV, dating back to epidemic cases in the 1950s, remaining a significant public health concern across the New World regions. AHF, a severe manifestation of JUNV infection, presents a complex clinical picture, with most patients experiencing debilitating symptoms and approximately one-third facing life-threatening complications, yet with an overall case-fatality rate around 15%, lower than some other viral hemorrhagic fevers. Notably, hepatic involvement in AHF caused by JUNV is comparatively minimal, distinguishing it from its counterparts, with patients often exhibiting relatively low viremia levels, and recovery coinciding with the development of neutralizing antibodies, underscoring the immune system's crucial role in combating the infection and emphasizing the necessity for ongoing research to deepen our understanding and enhance management strategies effectively.

IndexTerms - Calomys Musculus, Viral replication, Rodents, Hemorrhagic Fever, Virion

I. INTRODUCTION

Arenaviruses stand as harbingers of acute hemorrhagic fevers, casting formidable shadows over global public health. Epitomized by notorious strains like Lassa fever virus (LASV) in West Africa and Junin virus (JUNV) in Argentina's Pampas region, these pathogens paint a grim picture of infectious disease severity. Their intimate relationship with rodent reservoirs underscores the perpetual threat of zoonotic spillover, perpetuating a cycle of transmission that keeps communities on edge. Devoid of licensed vaccines or targeted antiviral therapies, these viruses loom large in the realm of biodefense, warranting meticulous planning and preparedness on a national scale.

Defined by an enveloped negative-sense RNA genome, arenaviruses orchestrate their replication dance exclusively within the cellular cytoplasm, setting the stage for a molecular saga of viral hijacking. Within this genomic blueprint lie the indispensable actors: the RNA-dependent RNA polymerase (L) and the nucleoprotein (N), masterminds of viral replication. Junin virus, architect of Argentine hemorrhagic fever's grim tale, etched its mark on history in the 1950s, targeting primarily the toil-worn hands of farm laborers. The choreography of its transmission unfolds intricately alongside the behavioral rhythms of its rodent cohorts, particularly *Calomys musculus*, whose peregrinations through cornfield hedgerows set the stage for human peril. The virion of Junin virus emerges as a sculpted enigma, donning shapes ranging from circular to pleomorphic, with dimensions stretching between 110 nm and 300 nm. Its single-stranded bi-segmented RNA genome, coupled with exterior projections reminiscent of hollow golf clubs, stamps its identity within the Arenaviridae family's diverse repertoire. Argentine hemorrhagic fever's toll, with mortality rates oscillating between 15% and 30%, paints a canvas of dread, where initial symptoms of headache pave a treacherous path towards debilitating manifestations like nausea, vomiting, and vertigo. In this intricate dance of pathogenesis, the Junin virus casts a unique shadow, urging relentless pursuit of understanding and vigilance in combating its lethal grip.

II. VIROLOGY

Within the intricate realm of virology, the Junin virus virion emerges as a captivating enigma, its enveloped form boasting a variable diameter spanning from 50 to 300 nm. Adorning its surface like sentinels, T-shaped glycoprotein extensions, reaching up

to 10 nm from the envelope, stand as pivotal mediators of attachment and cellular entry, orchestrating a delicate dance of infection within the host. Its genomic blueprint, a testament to nature's complexity, comprises two single-stranded RNA molecules, each bearing two distinct genes in an ambisense orientation, aptly labeled 'short (S)' and 'long (L)' due to their respective lengths. The S segment, approximately 3400 nucleotides long, weaves the tale of the nucleocapsid protein and the glycoprotein precursor (GPC), the latter cleaved to sculpt the viral glycoproteins GP1 and GP2, architects of the T-shaped glycoprotein spike adorning the virion's surface. Meanwhile, the L segment, stretching around 7200 nucleotides, encodes the viral polymerase alongside a zinc-binding companion, furthering the intricate machinery of viral replication. Amidst this biological ballet, rodents emerge as natural hosts, predominantly *Calomys musculinus* and *Calomys laucha*, though Junin virus antigens have also been unearthed in an eclectic array including *Akodon azarae*, *Bolomys obscurus*, *Mus musculus*, and *Oligoryzomys flavescens*. Humans, mere accidental voyagers in this microbial world, find themselves ensnared by Junin virus's treacherous grasp, while laboratory-bred mice, rats, guinea pigs, and non-human primates serve as willing acolytes in the pursuit of scientific understanding.



Fig 1 Structure of Argentine arenavirus

Among the NW arenaviruses, CHPV and SABV infections have only been identified as single incidents, whilst JUNV, MACV and GTOV have infected many people. The disease manifestations caused by infection with these viruses display many of the same symptoms observed with OW arenavirus-induced HF. Additional symptoms produced by JUNV infection, the most serious of the NW arenaviruses in terms of human infections, include mild hypotension and conjunctivitis. Neurological symptoms such as irritability, lethargy and hyporeflexia have also been observed.

III. EPIDEMIOLOGY

Virus, the landscapes of Argentina and Bolivia stand as the stage for its endemic theatrics, where the virus weaves its intricate tale of infection and resilience. An enigmatic presence in these regions, Junin virus finds its prime opportunity for dissemination during the fervent corn harvesting season, when the delicate equilibrium between man and rodent host, *Calomys callosus*, is disturbed amidst the rustling stalks of corn fields. Since its unveiling as Argentinian mammarenavirus in 1958, this viral entity has embarked on a geographical odyssey, expanding its dominion beyond the confines of its initial 15,000 km² realm. As the new millennium dawned, its reach extended tenfold, encompassing a staggering 150,000 km² expanse of reported cases, painting a portrait of viral expansion both remarkable and ominous, underscoring the dynamic interplay between pathogen, host, and environment in the ever-evolving tapestry of infectious disease epidemiology.

Aligned with the rhythm of the maize harvest, unfurling between April and July when rodent populations crescendo to their zenith, Junin virus finds fertile ground for its virulent symphony. The onset of its incidence, most fervently felt in nascently affected territories, heralds a crescendo of affliction followed by a gradual diminuendo in attack rates across subsequent years, marking the cyclical pulse of its endemic march. Within this ecological ballet, the absence of person-to-person transmission, likely due to the modest titers of circulating virus, veils the epidemic landscape in a cloak of relative containment. Yet, the relentless northward and eastward expansion of the endemic zone from Argentina's verdant Pampas region casts a shadow over some 5 million souls, ensnaring approximately one in five of the nation's populace in its perilous embrace. In the throes of major epidemics, meticulously timed to coincide with the maize harvest's crescendo, Argentina becomes the battleground where Junin virus unleashes its most fervent onslaught, with May standing as the zenith of its malevolent fervor. This disease, a fourfold scourge upon the male population compared to their female counterparts, finds its fertile ground among rural laborers, shunning the urban sanctuary. The annual ballet of affliction dances in lockstep with the local population densities of the drylands vesper mouse, *Calomys musculinus*, whose numbers serve as harbingers of human suffering. Amidst this tableau of affliction, the vaccination campaigns targeting the high-risk populace weave an intricate tapestry of altered epidemiological patterns, a testament to humanity's tenacious struggle against the encroaching shadows of disease.

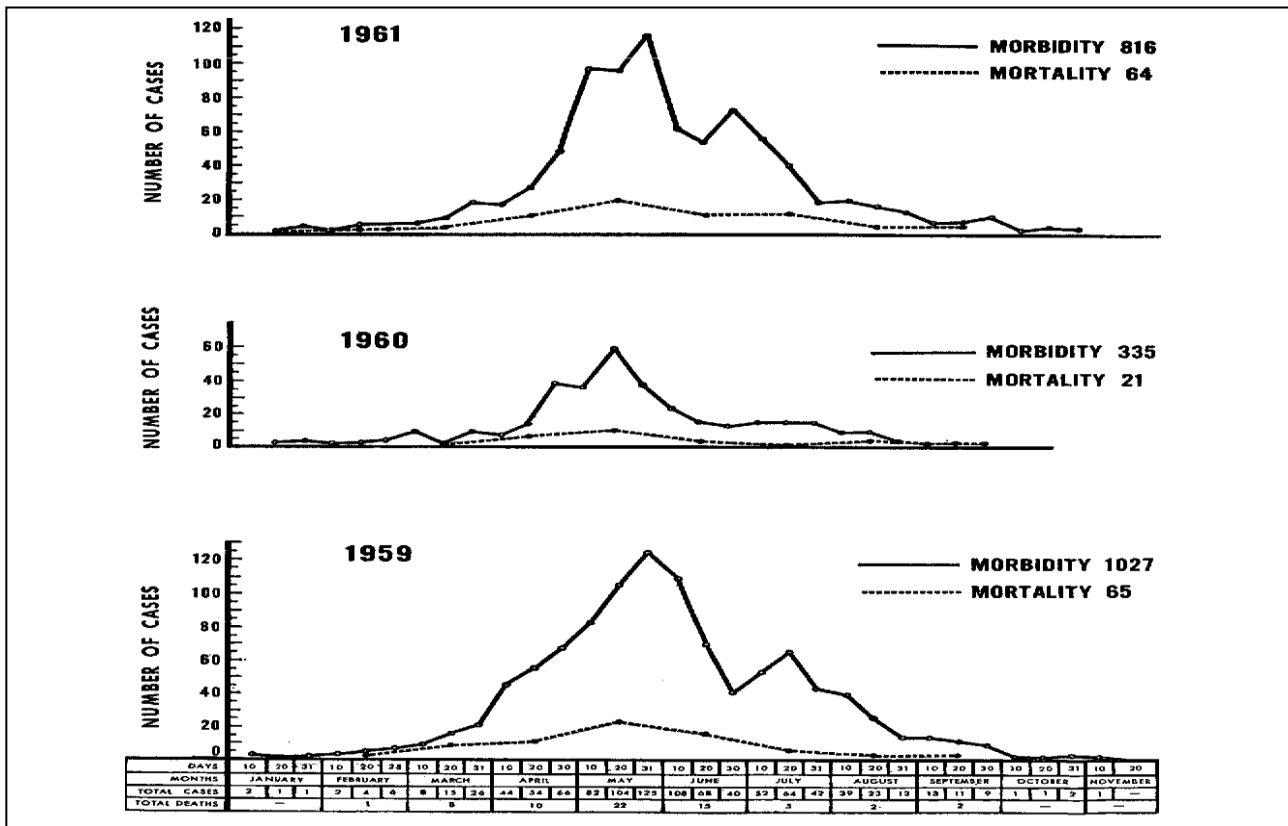


Fig 4 Morbidity & Mortality rate of Arenavirus yearwise data

IV. PATHOGENESIS

In the unfolding narrative of Junin virus's clinical saga, a symphony of symptoms unfolds, echoing the cadence of various infectious maladies yet bearing a distinctive imprint. From the onset, a mosaic of malaise, anorexia, chills, headache, myalgia, and fever paints a canvas of discomfort, heralding the prelude to a multifaceted symphony of constitutional, gastrointestinal, cardiovascular, and neurologic discord that crescendos in the days to come. What sets Junin virus apart lies in its chameleon-like adaptability, infiltrating the human domain through the skin, respiratory tract, or gastrointestinal mucosa, a testament to its cunning and versatile nature in orchestrating pathogenesis's intricate dance. As it proliferates within the host's sanctum, Junin virus orchestrates a silent dissemination, stealthily navigating through the body's corridors without leaving behind overt signs of its presence, unveiling a subtlety that belies the gravity of ensuing pathophysiological processes. At the microvascular frontier, Junin virus's impact reverberates with profound implications, as capillary dilatation unfurls its crimson tapestry alongside the remarkable spectacle of perivascular erythrocyte diapedesis and bleeding. This intricate choreography of vascular involvement, underscored by the curious phenomenon of minor edema within the vascular walls, distinguishes Junin virus's pathology with a signature both subtle and profound. Amidst this intricacy, the tableau of Argentine Hemorrhagic Fever (AHF) unfolds, a tapestry woven with a multifaceted interplay of thrombocytopenia, altered platelet function, and coagulation perturbations intertwined with the activation of fibrinolysis. This symphony of hemostatic irregularities, conducted by Junin virus's invisible hand, carries with it the pronounced involvement of endothelial cells, evidenced by heightened levels of von Willebrand factor, sculpting a unique and characteristic profile that sets AHF apart within the annals of infectious disease.

Upon successful clathrin-mediated endocytosis, the Junin Virus orchestrates a remarkable molecular symphony within the host cell. Activation of the PI3K/Akt signaling pathway propels the virus into a more acidic compartment of the endosome, setting the stage for a meticulously choreographed sequence of events. The viral RNA, with its 3' and 5' ends acting as a binding site, serves as a template for the initiation of transcription by viral polymerases. The NP protein takes the spotlight as the first translated protein, laying the foundation for subsequent steps in the viral life cycle.

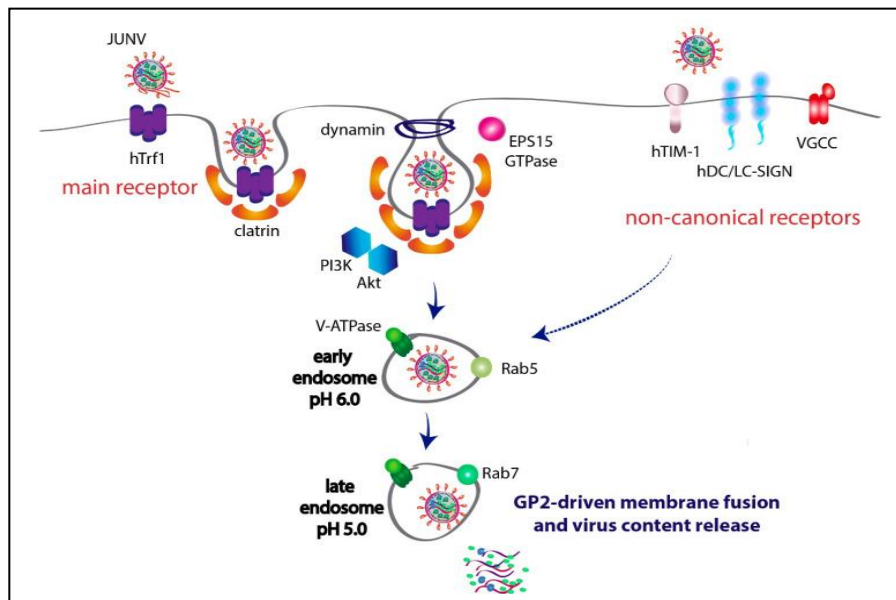


Fig 5 Pathogenesis & viral Replication in host tissues

In the intricate choreography of viral replication, a pivotal moment unfurls as the translation of the glycoprotein precursor (GPC) heralds its cleavage into the dynamic duo of GP1 and GP2, akin to protagonists poised for their entrance onto the viral stage. As GP1 strategically embeds itself in the peripheral membrane while GP2 integrates into the integral membrane, a symphony of recognition ensues, orchestrating the intricate dance of viral entry into host cells. Amidst this molecular theater, the cleavage of GPC unveils a molecular sentinel, the signal-stable peptide (SSP), poised to guide GPC's responsive adaptation to acidic conditions, a testament to the virus's adaptive prowess amidst the ever-changing host environment. As the viral polymerases, akin to master conductors, meticulously transcribe the RNA genome, a striking absence of the conventional 3'-polyA tail evokes intrigue, while the capping of newly synthesized strands on the 5' end adds a flourish of complexity to this molecular performance. With a stem-loop formation signaling the graceful conclusion of transcription, the daughter strands of viral RNA elegantly intertwine with other RNA types, setting the stage for the grand finale—the assembly of virions. In this symphony of assembly, the collaborative efforts of the N and Z proteins seamlessly orchestrate the intricate choreography of viral component assembly, with the Z protein assuming the mantle of principal conductor, guiding the majestic spectacle of viral budding from the host cell membrane, a sublime crescendo in the captivating drama of viral replication.

Table 1 Sign & Symptoms of Arenavirus

Sign/symptom	Old World		New World				
	LASV	LUJV	JUNV	MACV	GTOV	SABV	CHPV
Haemorrhage	Mild	Yes	Infrequent	Infrequent	Yes	Yes	Yes
Fever	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Leukopenia	Yes	Yes	Yes	Yes	Yes	Yes	–
Thrombocytopenia	infrequent	Yes	Yes	Yes	Yes	–	–
Oedema	Yes	Yes	Yes	Yes	Yes	Yes	–
Shock	Yes	–	Yes	Yes	Yes	Yes	–
Petechiae	Yes	Yes	Yes	Yes	Yes	Yes	–
Elevated AST/ALT*	Yes	Yes	Yes	Yes	Yes	Yes	–
Late neurological syndrome	No	–	Yes	–	–	–	–
Seizure	Yes	–	Yes	Yes	Yes	Yes	–
Respiratory distress	Yes	Yes	–	–	–	–	–
Myalgia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vomiting	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Arthralgia	Yes	–	Yes	Yes	Yes	–	Yes
Sensorineural deafness	Yes	–	No	No	No	–	–

Sign/symptom	Old World		New World				
	LASV	LUJV	JUNV	MACV	GTOV	SABV	CHPV
Hypotension	Yes	–	Yes	Yes	–	–	–
Vascular lesions	No	–	No	No	–	–	–
Elevated cytokines	No	–	Yes	Yes	–	–	–

V. DIAGNOSTICS

Navigating the diagnosis of Junin virus infection demands a nuanced approach, blending clinical acumen with specialized laboratory techniques. Here are distinctive strategies in unraveling the enigma of Argentine hemorrhagic fever (AHF): The diagnostic journey for Argentine hemorrhagic fever (AHF) begins with an intricate understanding of its clinical symphony, where fever, malaise, headache, myalgia, gastrointestinal nuances, and the specter of hemorrhagic manifestations form the narrative backdrop, guiding the initial diagnostic steps. This symphony is further enriched by the serological tapestry woven from the patient's serum, as ELISA and immunofluorescence assays meticulously unveil Junin virus-specific IgM and IgG antibodies, offering crucial insights into the diagnostic puzzle.

In the laboratory, the pursuit of the elusive Junin virus extends to specialized cell cultures, where delicate attempts are made to coax the virus into revealing itself from clinical specimens. Molecular revelations unfold through the precision of PCR, swiftly deciphering viral RNA akin to unraveling the genetic code of the clandestine invader. Immunohistochemistry provides a poignant voice to viral antigens in tissues, especially valuable in post-mortem examinations, adding layers to retrospective diagnostics.

At the point of care, elegance takes center stage with rapid diagnostic tests offering swift responses crucial in resource-limited settings. These tests, capable of detecting Junin virus or specific antibodies, provide a nimble approach to diagnosis. The diagnostic tapestry is further enriched by travel histories and exposure narratives, akin to detective stories, unraveling tales of journeys to endemic realms and potential encounters with rodent reservoirs, guiding the diagnostic voyage. Amidst this diagnostic choreography, a ballet of differential diagnosis distinguishes Junin virus infection from its viral counterparts and mimicking diseases, demanding astuteness and a discerning eye to reach a conclusive diagnosis.

VI. TREATMENT AND PREVENTION

Currently, there isn't a specific antiviral medication approved for treating infections caused by the Junin virus or Argentine Hemorrhagic Fever (AHF). However, patients diagnosed with AHF require comprehensive supportive care alongside symptom management. Careful monitoring and tailored supportive treatment are crucial for effectively managing symptoms and preventing further complications. This may include fluid and electrolyte restoration, organ failure management, addressing secondary infections, and correcting coagulation irregularities. In the realm of treating Argentine hemorrhagic fever caused by JUNV, convalescent plasma therapy stands as a notable treatment avenue. It holds the distinction of being the sole approved treatment for this ailment. Beyond its application in AHF, convalescent plasma therapy has demonstrated efficacy in addressing other viral infections like Ebola virus and SARS-CoV-2. Additionally, through a process involving immunization of mice with DNA followed by antibody screening against Glycoprotein Complex (GPC), researchers have identified a suite of monoclonal antibodies (mAbs). Among these, five mAbs emerged as particularly potent in neutralizing JUNV. Further scrutiny delved into their ability to bind conformational GPC and Glycoprotein 1 (GP1), with a keen focus on the latter's significance in receptor recognition.

Preventing Junin virus (JUNV) infection primarily involves implementing rigorous measures to minimize exposure to the virus and adopting preventive practices to halt its transmission. Firstly, promoting awareness about the virus and its modes of transmission is essential. Educating communities residing in endemic areas about the risks associated with contact with rodents, particularly the *Calomys musculinus* species, which serves as the primary reservoir, is crucial. Encouraging proper sanitation practices, such as storing food in rodent-proof containers and maintaining clean living environments, can help reduce the likelihood of rodent infestations. Secondly, implementing vector control strategies to manage the population of the primary vector, the *Calomys musculinus* species, is vital. This may involve measures such as rodent-proofing buildings, using insecticides to control rodent populations, and implementing environmental management techniques to reduce rodent habitats. Additionally, vaccination programs for individuals at high risk of exposure, such as agricultural workers and laboratory personnel, could be considered to provide an additional layer of protection against JUNV infection.

So generally, a multifaceted approach encompassing public education, sanitation measures, vector control, and vaccination efforts is essential to effectively prevent the spread of Junin virus and reduce the incidence of Argentine Hemorrhagic Fever.

VII. PUBLIC HEALTH IMPLICATIONS

The Junin virus, responsible for Argentine hemorrhagic fever (AHF), presents substantial public health concerns, especially in endemic regions. Its capacity to induce severe illness, including hemorrhagic manifestations, underscores the urgency for effective control measures. Primarily transmitted through contact with infected rodents, particularly the *Calomys musculinus* species, Junin virus control efforts focus on rodent management and community education. In healthcare settings, where transmission risks are heightened, stringent infection control measures are imperative to safeguard healthcare workers and patients. Moreover, the potential for outbreaks necessitates robust surveillance and rapid response protocols. International collaboration is pivotal in addressing the evolving threat posed by Junin virus, emphasizing the importance of sharing knowledge and resources. Overall, a comprehensive approach integrating surveillance, prevention, and international cooperation is essential in mitigating the public health impact of Junin virus.

Continuous research and vigilant surveillance are crucial in deepening our understanding of the Junin virus and Argentine hemorrhagic fever (AHF). Investigating virus biology, transmission dynamics, and genetic diversity is essential for developing targeted therapeutics and vaccines. Enhanced surveillance methods are necessary to track virus transmission and detect outbreaks early. Improving diagnostic tools and understanding host immune responses can guide treatment and prevention strategies. Evaluating public health interventions like rodent control and vaccination programs is essential for effective disease management. Collaborative efforts involving multidisciplinary teams are vital for addressing the complex challenges posed by Junin virus and advancing control strategies.

VIII. CONCLUSION

In conclusion, the study of the Junin Virus encompasses various areas including viral replication mechanisms, host-virus interactions, therapy, and immunization. Recent evidence suggests that the Z protein of the Junin virus can interact with human ribosomal proteins, Ras proteins, endosome sorting proteins, and ATP production proteins during infection. Additionally, the virus has been shown to bind with human Type 1 Interferon, which may contribute to triggering Argentine Hemorrhagic Fever (AHF) once inside a cell. Studies in mice have indicated a correlation between the severity of AHF symptoms and the levels of Type 1 Interferon in the blood. Understanding these mechanisms provides insights for developing improved treatment and immunization strategies. Research is also underway on antibodies against the Junin Virus, with promising results showing that the virus's glycoprotein could potentially provide protection against other New World arenaviruses like Machupo. These findings not only hold promise for enhancing public health in Argentina but also contribute to the broader understanding of vaccine development against various viruses. This ongoing research highlights the importance of continued efforts to combat emerging infectious diseases effectively.

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