A General Review on Hantaviruses

Gandi UmaRani1, M.Monalisa[2], Tejasree[3]
[1,2,3]*Department of pharmaceutics, RBVRR Women's college of Pharmacy, Affiliated to Osmania University, Hyderabad, Telangana, India*

Abstract **- Hantaviruses are enveloped negative single-stranded RNA viruses belongs to Hantaviridae family, it was hosted by small rodents and entering into the human body through inhalation. Hanta virus also cause Hantavirus pulmonary syndrome (HPS) hemorrhagic fever with renal syndrome (HFRS) and it also known as Hantavirus cardiopulmonary syndrome (HCPS). Hantaviruses and its mortality rate is 35%–40%. Virus infect more than 200 000 people annually all around the world. Mainly viruses impair the honor of endothelial barrier due to an immoderate the immune response that is proposed to be central in the pathogenesis and is a hallmark of hanta virus disease. Different diagnostic tools including polymerase chain reaction (PCR), focus reduction neutralization test (FRNT), enzyme-linked immunosorbent assay (ELISA), immune blot assay (IBA), immune fluorescence assay (IFA). Now we must have the availability of therapeutic modalities is the major challenge to control this deadly virus why means still no FDA approved drug or vaccine is available for hanta virus. DNA-based vaccines, anti-viral agents, monoclonal and polyclonal antibodies are neutralized the viruses. So these techniques as the hope for the treatment of Hantavirus disease. This review has been to provide an overview of hanta viruses' disease, its diagnostic tools, Patho physiology and the treatment approaches to control the Hantavirus infection.**

Index Terms **- Hanta virus, hanta viridae family, HFRS, HPS.**

INTRODUCTION

Hantaviruses first found in Europe and Asia, predominantly also known as Old World Hantaviruses. It was also known as ortho Hantaviruses appear to be hosted by small rodents. It was a single stand RNA virus and it was belong to hantaviridae family. These viruses affect approximately 150 000–200 000 people annually worldwide.

Hantaviruses are produces numerous copies of nucleoprotein and the viruses RNA is comprised of three segments of negative-stranded RNA:

- The largest segment is RNA polymerase
- The middle segment is glycol proteins.
- The smallest is nucleocapsid protein.

SPECIES OF HANTA VIRUS

About 40 species of Hantaviruses have been identified and 22 species are considered pathogenic to humans and all have rodents as reservoirs, hanta virus cause the HFRS with mortality rate ranging from <1% to 15% and the most common are Puumala virus (PUUV), Dobrava–Belgrade virus (DOBV) and Hantaan virus (HTNV). Seoul virus (SEOV), an HFRS-causing Hantavirus carried by the Norway rat (Rattus norvegicus) has a widespread distribution coinciding with transportation of this rodent reservoir worldwide. New World Hantaviruses reported in America include Sin Nombre virus (SNV) and Andes virus (ANDV), and Choclo virus (CHOV) reported from Central America and produce the hantavirus pulmonary syndrome (HPS) with a mortality rate >40%.3 Due to variation in the distribution of rodents as viral reservoirs worldwide, the human infections from these pathogenic Hantaviruses are typically restricted and to date only ANDV infection has been reported as transmittable from human to human.4
Hantavirus caused by zoonotic diseases has serious clinical signs related to kidney failure, respiratory disorders, cardiac disease, muscular disorders and fever.5 Haemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) also known as hantavirus cardiopulmonary syndrome (HCPS) are the most serious disorders that have developed due to hantaviruses. HPS and HFRS are initially recognized with severe fever, lethargy, and respiratory distress, stomach issues including diarrhoea, nausea and vomiting. For the management of Hantavirus worldwide, there is a need for medical counter measures for the prevention and treatment of Hantavirus infection. For hanta virus there is no drug

or vaccine was approved by FDA. Therefore, this review article aimed to provide scientific information about the infection, pathophysiology, rodent reservoirs distribution worldwide, diagnosis and therapeutic approaches related to Hantavirus.

HFRS AND HPS HISTORICAL PROSPECTIVE17

This virus infection produced world attention during the Korean conflict (1950–1953), although the resembling disease was found to have been reported 900 years ago in Chinese writings. Hantavirus infected more than 3000 United Nations. It was commonly referred as haemorrhagic fever with renal syndrome (HFRS) but at that time the agent responsible for this infectious disease remained unknown until the early 1970s, when Lee et al, reported the presence of Hantaan virus (HTNV), in the lungs of the striped field mouse (Apodemus agrarius) as its natural reservoir.14
In early 1930s the milder form of HFRS known as nephropathia epidemica (NE), was reported in Fennoscandia and in 1980 its causative agent Puumala virus (PUUV) was investigated present in bank voles (Myodes glareolus) in Finland.15 After that a large outbreak of Hantavirus infection in 1993 was reported in the Four Corners region of the USA, where the respiratory distress related disease named hantavirus cardiopulmonary syndrome (HCPS) occurred16 and the two aetiological agents including Sin Nombre virus (SNV) and Andes virus (ANDV) were found in North and South America.
Both HFRS and HCPS diseases are acute febrile infections which are transmitted into the human body through the inhalation of aerosols or dust particles containing the virus particles from infected rodent excreta. Kidney failure and haemorrhagic indices range from mild to severe petechiae resulting in severe internal bleeding are the major characteristics of HFRS while HCPS is characterized by pneumonia and cardiovascular dysfunction. During the progress of infection, it leads to the rise of permeability of the microvascular endothelium as a common effect of hantavirus infection. Moreover host immune system played major role in the pathogenesis of hantavirus infection instead of direct viral cytopathology. In other countries, Hantaviral infections are undetected. So additional hantaviruses may remain undiscovered. So that Hantaviruses and the diseases produced by them required the consideration of researchers, public health officials and physicians awareness with regard to their impact on public health.

ECOLOGY AND EPIDEMIOLOGY24,18

Hanta virus like some of other Bunyaviruses, hantaviruses are also sustained and transmitted through different types of mammalian host reservoirs like shrews and moles (order Soricomorpha), bats (order Chiroptera), and rodents (order Rodentia).
Hantaviruses are divided into three major species based on the rodent as their reservoir hosts:
1. Old World viruses like HTNV, SEOV and DOBV causing HFRS that are carried in Murinae rodents found in Europe and Asia predominantly.
2. New World viruses like SNV, New York-1 virus (NY-1V), and ANDV producing HPS that are harbored by the Sigmodontinae sub-family members particularly reported in America. and
3. Hantaviruses reported both in Old or New World and related with mild disease include PUUV or Prospect Hill virus (PHV) and Tula virus (TULV) (non-virulent Hantaviruses) are hosted by Arvicolinae rodents.
Phylogenetic analyses reveal the initiation of Hantaviruses from bats, shrews, or moles and later on recognized in rodents persistently and Hantaviruses further separated as rodent population's endured geographic divergent and differing evolution. Some reports are providing the evidence related to shrew-borne Hantavirus infection in humans.
Hantavirus infection in human is characterized by fever is high-grade, muscular pain, gastrointestinal symptoms, and, most notably, vascular leakage. Some researchers have considered that HFRS and HPS are single diseases because both share similar underlying pathology and clinical features such as vascular leakage and thrombocytopenia. But in HFRS renal involvement is more significant such as oliguria and renal failure while in HPS pulmonary symptoms are more prominent and pulmonary oedema is reported in many patients.

HANTAVIRUS LIFE CYCLE/ HANTAVIRUS TRANSMISSION AND REPLICATION5

Hantaviruses it was transmitted from aerosolized rats excreta. Life cycle occur by close contact among tainted and naïve rodents; transmission has

additionally been hypothesized to occur through battling, gnawing, and sexual conduct. Complete catch and discharge ponders performed with existing populations of SNV tainted Peromyscus maniculatus (deer mice) showed that SNV disease does not occur in infant or weanling deer mice. Recently, hantavirus infection was also reported in many domestic animals species (eg, pigs, cats, rabbits, dogs) as well Hantavirus replication takes place in vascular endothelial cells and macrophages particularly in the lung and the kidney. For pathogenic hanta viruses, the transmission into host cells occurs via connection to αγβ3 integrin on the cell surface resulting in consequent endocytosis.

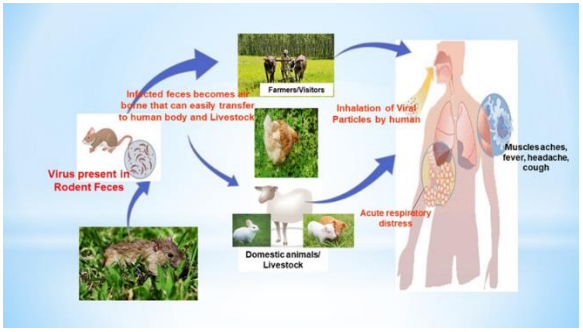

Figure 1: Transmission of hantavirus takes place by means of inward breath of aerosolized viral particles in the urine, defecation, and salivation discharged into the environment.

Replication cycle main step is the attachment with virus molecule to cell's surface by interaction with viral glycoprotein and host's cell surface receptors.

1. Passage through receptor-intervened endocytosis and uncoating occurred and releasing of viral genomes quickly.
2. Complementary RNA is transcripted from viral RNA (VRNA) by genome utilization host primers.
3. By using host apparatus S, L and M, messenger RNA (mRNA) is translated.
4. Viral RNA is transcripted and amplified by connecting with N protein and is transported to Golgi apparatus.
5. All components are assembled at one point Golgi apparatus otherwise in new world Hantaviruses at plasma membrane.
6. Last step is virus egress fusion and Golgi vesicles possess mature viral components with plasma membrane

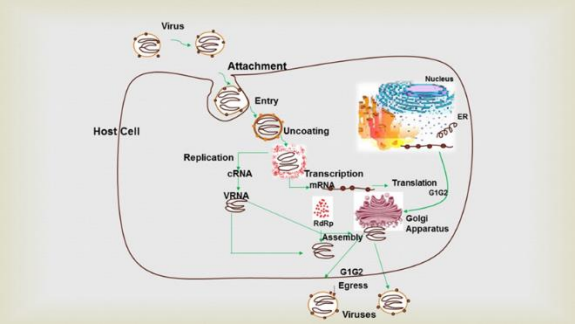

Figure 2: hanta virus replication

PATHOPHYSIOLOGY OF HANTAVIRUS DISEASES 6, 7

Pathophysiology of hantavirus antigens have the capability to enter many body organs, kidneys or lungs endothelial cells and macrophages are the major cells both in animals and humans where hantavirus infect. Many types of cytokines and endothelial adhesion molecules are expressed in the peritubular area of the distal nephron. However, the dissemination of Hantavirus after inhalation into the human body is not yet completely cleared, β-integrin receptors at the target cell membrane and viral proteins Gn and Gc interaction take place. Both virulent (SEOV, HTNV, SNV, PUUV) and non-virulent (Prospect Hill virus, Tula virus,) Hantaviruses have the ability to infect the endothelial cells but through different integrin receptors (αvβ1 vs α5 β3). Expression of β3-integrin receptors on immature dendritic cells contribute significantly in the dissemination of hantavirus and also serve as vehicles for virion entry into endothelial cell through the lymphatic vessels to the regional lymph nodes. These endothelial cells provide the shelter for the replication of virus, which activate the immune system particularly through macrophages and CD8 + T cells. Moreover, delayed type I interferon response generated higher pathogenic viral load in infected cells and intensifying response in the form of inflammatory cytokine and chemokines from immune system makes the condition unfavorable. It was reported that both in DOBV and PUUV infection, the level of serum interleukin-10, interferon-γ and tumour necrosis factor-α (TNF-α) increased significantly. Increased level of IL-6 and TNF-α as proinflammatory cytokines and low level of immunosuppressive transforming growth factor-β1 are characteristics of the severity of NE disease. Further, cytotoxic T cells

play a vital role in the destruction of capillaries via immunopathology in NE patients, also by increased concentrations of nitric oxide and TNF-α, and compared to other haemorrhagic fever viruses, Hantaviruses induce the dendritic cells growth and further intensify the T-cell response during acute infection. High T-lymphocytes activity induces the CD8 + T cells and suppresses CD4+ vs CD8 + T-cell ratio, in NE patients, which coincides with the onset of clinical disease58 and the extensive immune response imposes a severe harmful impact in HFRS-infected patients.53 It might be proposed that Hantavirus pathophysiology is a multifactorial process with complex factors including deregulation of endothelial cell barrier functions, contributions from immune responses and platelet dysfunction. Moreover, HLA type as genetic predisposition association with severe HFRS disease was also reported and it was found that different hantaviruses were associated with different HLA haplotypes. Haplotype HLA-B*8 DRB1*03:02, a genetic predisposition was found to be associated with a severe form of HFRS due to PUUV infection and the same HLA haplotype was linked with the infection of ANDV for the development of severe HCPS. In addition, it was reported that in patients with DOBV infection HLA haplotype HLA-B*35 was associated with the progression of severe disease60 and this HLA haplotype is correlated with severe HCPS due to SNV.

DIAGNOSTIC FEATURES FOR HANTAVIRUS DISEASE 15

Diagnosis of acute Hantavirus infection is based on serology as virtually all patients have Immunoglobulin M (IgM) and usually also Immunoglobulin G (IgG) antibodies, and the Hantavirus infection can also be confirmed by the detection of Hantavirus genome in blood or serum samples by RT-PCR. Both traditional and quantitative RT-PCR tests are used to detect viraemia.Virus isolation in cell culture is also used to identify the Hantavirus in tissue samples. The most common methodology for the determination of Hantavirus disease depends on serologic tests. The 3 basic proteins of hantaviruses (Gn, Gc and N) can initiate an abnormal state of IgM antibodies, which are recognizable at the beginning of infection manifestations and includes enzyme-linked immunosorbent assay (ELISA), immune fluorescence assay (IFA), immunoblot assay (IBA) and focus reduction neutralization test (FRNT).

THERAPEUTIC APPROACHES TO CONTROL HANTAVIRUS 3, 11

Medicines can be given either as a therapeutic agent or as prophylactic post-exposure. After infected by a viral infection, post-exposure prophylactics are administered before the occurrence of clinical signs or viremia. The therapeutic strategy is usually related to causes, whether clinical signs arise or viremia is observed. Medicines or vaccine are not approved by FDA. Hence some of the following are the therapeutic approaches used to manage the Hantavirus diseases.

1. Antiviral agents target the host or boost host immune system: Antiviral agents like Corticosteroids it has high concentrations of proinflammatory cytokines, specifically TNF-α, have been identified in sera of HFRS and HCPS patients.
2. Inhibitors prevent host-cell hantavirus-binding: Pathogenic hantaviruses bind the αvβ3 integrin to the outer surface of host cells.
3. Monoclonal antibodies as therapeutic agents

During the 1980s, multiple monoclonal HTNV antibodies were named to identify glycoprotein, Gn and Gc neutralization sites. Monoclonal antibodies were tested by passive transmission in a series of epitopes that associate similar viral epitopes with HTNV protection. The experiment has shown that 15 monoclonal anti-corporeal antibodies tested are enough to avoid HTNV infection in hamsters with neutralizing antibody reaction either to the Gn or Gc only.

4. Polyclonal antibodies as therapeutic agents

Andes virus/hamster lethal disease mode and SNV/deer-mouse-infection model85, 86 protect animals by administering human convalescent plasma, showing that neutralizing antibodies is adequate for protection.

Some other Antiviral agents target the Hantavirus is ribavirus

11Ribavirin was administered to suckling mice after the initiation of clinical symptoms was eventually found to suppress Hanta virus replication in vitro decreasing the viral risk as well as lethality as opposed

to control animals by 45%. A common finding in both studies is that ribavirin as therapeutic is expected to be ineffective one HPS develops into the cardiopulmonary phase.

Lactoferrin;

A single report has examined the effects of lactoferrin, iron-binding glycoprotein, in the suckling mice for the HFRS prevention. Lactoferrin–ribavirin combination was necessary for focus inhibition. The lactoferrin levels of 40 and 160 mg/kg administered as two doses in vivo SEOV/suckling mice model, respectively, resulted in 85% and 94% survival since treatment started before the virus challenge.

ETAR

Nucleoside analogue ETAR showed activity against HTNV and ANDV. The HTNV/suckling mouse model was tested for in vivo efficacy. Ten days after HTNV challenge, a 15-day statistically meaningful increase in stability happened for mice, either 12.5 or 25 mg/kg ETAR.

Favipiravir

Favipiravir (derivative of pyrazine) had anti-influenza properties, was now estimated having antiviral activity as well against arena viruses and bunya viruses panel. In vivo and in infection model of SNV/hamster along with lethal disease models of ANDV/hamster, favipiravir was tested. SNV RNA and lungs SNV antigen decreased by 100 mg/kg/d favipiravir oral ingestion two times daily.92 Likewise, blood and lungs detection of ANDV RNA and antigen in the lung is decreased by oral administration of 100 mg/kg/d of favipiravir two times daily, leading to 100% survival. ANDV/hamster model did not protect delayed antiviral therapy in accordance with other studies after viremia began.

PREVENTIVE MEASURES 13

Preventive measures depend on keeping away from exposure to rodents with hantavirus and their defecation, urine, substantial emissions and tissues.

Precautionary measures include the following steps: exhausting out the room before starting clean up, wetting the infected zone with commercial disinfectant or dye, and wearing defensive clothes and gloves. Wet paper towels or wet wiping are for the most part prescribed as cleaning techniques; methodology that avoids aerosolizing the viral infection during cleaning.

Individuals who have been occupationally presented to rodents should take precautionary measures to abstain from exposure. Based upon the conditions, this may incorporate gloves, rain boots, goggles, coveralls or outfit and additionally a respirator. Commercially inactivated vaccines for haemorrhagic fever with renal syndrome brought about by Hanta virus and additionally Seoul Viruses are provided in South Korea and China. Both all-inclusive precautions and droplet precautionary measures are presently suggested while treating patients infested with ANDV.

CONCLUSION

By seeing over all conclusion for hantaviruses is. This virus mainly hosted by small rodents and enter into the human body through inhalation causing haemorrhagic fever with renal syndrome (HFRS), hantavirus pulmonary syndrome (HPS) also known as hantavirus cardiopulmonary syndrome (HCPS). This virus infectes more than 200 000 people all around the world annually with a mortality rate upto 40%. Hantavirus shows a significant role in affecting target cells because it inhibits apoptotic factor in these cells and integrity impairment of endothelial barrier due to an excessive innate immune response which is proposed to be central to pathogenesis and is a hallmark of hantavirus disease. There is no vaccine or drug was approved by FDA. This review has been to provide an overview of hanta viruse disease, its diagnostic tools, Pathophysiology and the treatment approaches to control the hantavirus infection

REFERENCES

[1] Schmaljohn CS, Nichol ST. Bunyaviridae. In DM Knipe PM Howley eds. Fields Virology. Philadelphia, PA: Lippincott, Williams & Wilkins; 2007; 1741– 1789.

[2] Lin X-D, Guo W-P, Wang W, et al. Migration of Norway rats resulted in the worldwide distribution of Seoul hantavirus today. J Virol. 2012; 86(2): 972- 981.

[3] Jonsson CB, Hooper J, Mertz G. Treatment of hantavirus pulmonary syndrome. Antiviral Res. 2008; 78(1): 162- 169.

[4] Martinez-Valdebenito C, Calvo M, Vial C, et al. Person-to-person household and nosocomial transmission of Andes hantavirus, Southern Chile, 2011. Emerging Infect Dis. 2014; 20(10): 1629.
[5] Strand TM, Lundkvist Å. Rat-borne diseases at the horizon. A systematic review on infectious agents carried by rats in Europe 1995–2016. Infect Ecol Epidemiol. 2019; 9(1): 1553461.
[6] Krautkrämer E, Zeier M, Plyusnin A. Hantavirus infection: an emerging infectious disease causing acute renal failure. Kidney Int. 2013; 83(1): 23- 27.
[7] Llah ST, Mir S, Sharif S, Khan S, Mir MA. Hantavirus induced cardiopulmonary syndrome: a public health concern. J Med Virol. 2018; 90(6): 1003- 1009.
[8] Vaheri A, Strandin T, Hepojoki J, et al. Uncovering the mysteries of hantavirus infections. Nat Rev Microbiol. 2013; 11(8): 539- 550.
[9] Ahn C, Cho JT, Lee J, et al. Detection of Hantaan and Seoul viruses by reverse transcriptase-polymerase chain reaction (RT-PCR) and restriction fragment length polymorphism (RFLP) in renal syndrome patients with hemorrhagic fever. Clin Nephrol. 2000; 53(2): 79- 89.
[10] Aitichou M, Saleh SS, McElroy AK, Schmaljohn C, Ibrahim MS. Identification of Dobrava, Hantaan, Seoul, and Puumala viruses by one-step real-time RT-PCR. J Virol Methods. 2005; 124(1-2): 21- 26.
[11] Ogg M, Jonsson CB, Camp JV, Hooper JW. Ribavirin protects Syrian hamsters against lethal hantavirus pulmonary syndrome—after intranasal exposure to Andes virus. Viruses. 2013; 5(11): 2704- 2720.
[12] Cosson J-F, Picardeau M, Mielcarek M, et al. Epidemiology of Leptospira transmitted by rodents in Southeast Asia. PLoS Negl Trop Dis. 2014; 8(6):e2902.
[13] Brocato RL, Hooper JW. Progress on the prevention and treatment of hantavirus disease. Viruses. 2019; 11(7): 610.
[14] Lee HW, Lee PW, Johnson KM. Isolation of the etiologic agent of Korean hemorrhagic fever. J Infect Dis. 1978; 137(3): 298- 308.
[15] Brummer-Korvenkontio M, Vaheri A, Hovi T, et al. Nephropathia epidemica: detection of antigen in bank voles and serologic diagnosis of human infection. J Infect Dis. 1980; 141(2): 131- 134.
[16] Nichol ST, Spiropoulou CF, Morzunov S, et al. Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. Science. 1993; 262(5135): 914- 917.
[17] Vapalahti O, Mustonen J, Lundkvist Å, Henttonen H, Plyusnin A, Vaheri A. Hantavirus infections in Europe. Lancet Infect Dis. 2003; 3(10): 653- 661.
[18] Jonsson CB, Figueiredo LTM, Vapalahti O. A global perspective on hantavirus ecology, epidemiology, and disease. Clin Microbiol Rev. 2010; 23(2): 412- 441.
[19] Klempa B. Hantaviruses and climate change. Clin Microbiol Infect. 2009; 15(6): 518- 523.
[20] Kerins JL, Koske SE, Kazmierczak J, et al. Outbreak of Seoul virus among rats and rat owners—United States and Canada, 2017. Morb Mortal Weekly Rep. 2018; 67(4): 131.
[21] Yanagihara R, Gu SH, Arai S, Kang HJ, Song J-W. Hantaviruses: rediscovery and new beginnings. Virus Res. 2014; 187: 6- 14
[22] Zhang Y-Z. Discovery of hantaviruses in bats and insectivores and the evolution of the genus Hantavirus. Virus Res. 2014; 187: 15- 21.
[23] Zhang Y-Z, Zhang F-X, Gao N, et al. Hantaviruses in rodents and humans, inner Mongolia Autonomous region, China. Emerging Infect Dis. 2009; 15(6): 885.
[24] Meyer BJ, Schmaljohn CS. Persistent hantavirus infections: characteristics and mechanisms. Trends Microbiol. 2000; 8(2): 61- 67.