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A REVIEW ON HANTA VIRUS INFECTION ASSOCIATED WITH SPECTRUM OF DISEASE AND THEIR PREVENTION

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ABSTRACT

Hantaviruses are single-stranded, negative-sense RNA viruses that cause hemorrhagic fever, hantavirus renal syndrome (HFRS), or hantavirus cardiopulmonary syndrome (HFPS) in humans. More than 50% of the macromolecules in a virion are proteins, followed by 20–30% fat, 7% carbohydrates, and 2% RNA. Unlike other bunyavirus transmission, the hantavirus transmission depends on this trait. As a result, the virus can be taken up by a clathrin-coated vesicle (CCV), which is made of clathrin-coated cellular membrane. The most frequent sign is pulmonary edoema. Hospitalisation and inappropriate antibiotic use were significantly reduced as a result of early Hantavirus infection nephropathy epidemic diagnosis. Controlling rodents in houses and other locations where there are human activities happening is the most important step in the illness and prevention process.

KEYWORDS: Bunyaviridae, cardiopulmonarysyndrome, Hanta virus, Hanta virus cardiopulmonary syndrome, Hemorrhagic fever with renal syndrome, Puumala virus.

INTRODUCTION

Hantaviruses are negative-sense, single-stranded RNA viruses with small (S), middle (M), and large (L) segments. Hantaviruses linked to human diseases produce either hemorrhagic fever or with renal syndrome (HFRS) or hantavirus cardiopulmonary syndrome (HFPS) (HCPS).[11] Rodent-derived hantaviruses (HVs) and arenaviruses (AreVs) are significant pathogens. Phylogroup III HVs (HTNV, SEOV, etc.) are strictly related to the subfamilies of their hosts. whilephylogroup IV HVs (Sin Nombre virus, Andes virus, PUUV, Tula virus, etc are related toSigmodontinae and Arvicolinae These rodent-borne HVs are members of the Hantaviridae family. are classified into three evolutionary clades.[2] 23 hantaviruses, a genus of single-stranded RNA viruses of the Bunyaviridae family are the culprits. Hantaviruses that are harmful to humans arestored in rodents.[3] Hantavirus pulmonary syndrome (HPS) is an acute viral illness.characterised by a vague febrile illness that advances to severe noncardiogenic pulmonary edoema and cardiogenic shock The term "hantavirus cardiopulmonary syndrome" is another name for it. A vague term describes an acute viral infection known as hantavirus pulmonary syndrome (HPS). febrile illness that progresses to severe noncardiogenic pulmonary emphysema and cardiogenicshock. The term "hantavirus cardiopulmonary syndrome" is another name for it.[4] It causes acute pneumonitis. Deer mice are affected by the Four Corners virus, which is also known as Muerto. The transmission of Canyon and Sin Nombre viruses (Peromyscusmaniculatus) to humans is possible. result in a condition characterised by pre-four terminal cardiac dysrhythmias and widespread noncardiogenic pulmonary edoema, vascular volume contraction with hemoconcentration, lactic acidosis, and fast developing respiratory distress.[6] Hantavirus is an infection transmitted by aerosol from infected rats (contaminated by droppings, saliva, or inhalation) that can infect dogs, cats, sheep, or cattle. The Hanta virus does not cause any disease in rodents, but it is transmitted through even faecal matter.[7]

The first evidence of hantavirus infections in the Caribbean was found in Barbados.among human patients suspected of having leptospirosis, as well as rats (Rattus spp.), even though the identification of the hantavirus strain(s) is still uncertain. Climate change can have a consequence on hantavirus transmission and circulation in nature by impacting hantavirus Large rodent populations can be found in reservoirs. [15]Hantaviruses (family Hantaviridae) are negative-stranded, enveloped, monopartite RNA viruses ofthe order Bunyavirales New World hantaviruses (e.g., Andes virus, ANDV, Sin Nombre virus,and SNV) typically cause a severe syndrome with pneumonia and cardiopulmonary dysfunction.(i.e., hantavirus cardiopulmonary syndrome,

or HCPS) [17].Orthohantavirus diseases are classified into two types based on the organs involved and the location.region: hemorrhagic fever with renal syndrome (HFRS), which occurs primarily in Asia andEurope and is caused by "Old World"orthohantaviruses and hantavirus cardiopulmonarysyndrome (HCPS), which occurs in North and South America and is caused by the "New World."orthohantaviruses. Incubation times for new-world orthohantaviruses range from 7 to 49 days. HCPS is one of the most lethal infectious diseases; unfortunately, no drugs have proven efficacy.for HCPS exists.

Critical care support, including extracorporeal membrane oxygenation, is used intreatment (ECMO).[19] Nephropathiaepidemica (NE) is a mild form of hemorrhagic fever that is accompanied by renalsyndrome (HFRS). The puumalahantavirus causes it (PUUV), and the bank vole (Myodesglareolus) eats it.carries the PUUV infection, which is transmitted to humans by inhaling aerosols of infected rodent excreta [21]This research focuses on nucleoprotein N, one of the PUUV's key structural proteins. To assessthe dynamics of N localization and trafficking in live-cell experiments, we created chimericproteins with fluorescent proteins fused to the N-terminus of N.In expressing cells, YFP-Nrapidly clusters, eventually forming macromolecular complexes that can extend through themajority of the cell body. We also found preferential co-localization with P-bodies, actin, andvimentin but not tubulin, indicating a preference for cytoskeleton components. Strong spatialA correlation was found in the perinuclear region when co-expressed with other structural PUUVs.proteins, the glycoproteinsGc and Gn, indicating nascent virus assembly processes. Finally, weobserved large-scale oligomerization in fluorescence fluctuation spectroscopyexperiments.[22]

Generation of Fluorescently Labeled Hantavirus N Protein: Vero E6 cells were infected with the Puumalavirus, strain Sotkamo (V-2969/81), which is an orthohantavirus from the family of the Hantaviridae[22] Dulbecco's Modified Eagle's Medium (DMEM, PAA) is used for cell culture and transfection. Laboratories GmbH, Austria) was used to maintain Chinese hamster ovary (CHO-K1) cells and African green monkey kidney epithelial cells (Vero E6 cells) It was enhanced with 10%2 mM L-glutamine, 100 U/mL penicillin, and 100 g/mL streptomycin (all from foetal bovine serum) PAA Laboratories GmbH, Pasching, Austria). Then, 24 to 48 hours before imaging studies, expression The Turbofecttransfectionmethod was used to transfect plasmids into pre-plated cells. Thermo Scientific (Waltham, MA, USA) onto 35-mm glass-bottom microwell dishes (MatTek) Corporation, Ashlands, Massachusetts, USA). All cell lines other than CHO-K1 were plated on 18-mm glass cover slips (#1.5, Menzel, Thermo Scientific, Waltham, MA, USA) in a typical 12-well tissue culture plate Greiner, Kremsmünster, Austria[23] Ten different bat-borne hantaviruses have been described in 14 bat species in Asia, Europe, and North America. Africa. Bat-borne hantaviruses are genetically different from orthohantaviruses and belong to the Loanvirus and Mobatvirus are members of the Hantaviridae family.[24] There is still no clear understanding of the pathophysiology of HFRS. One of the potential causes of vascular hyperpermeability is VEcadherin cell signaling, and bradykinin may have a significant impact on microvascularhyperpermeabilityIcatibant, a bradykinin antagonist, was It was successfully used to treat viruses 2022, 14 and 2247.2 of 17 patients in Europe had severe HFRS caused by Puumala virus infection, also thought to be linked to the Inflammatory cytokines are involved in the pathophysiology of the hantavirus. The key to cytokine release syndrome or cytokine storm, which leads to more inflammatory cytokine outbursts, is interleukin-6. (IL-6).[25] Following HTNV infection, both CD4+T cells and CD8+T cells multiplied in the peripheral blood of HFRS patients and mounted protective immune responses.[10, 11] Additionally, Several studies have suggested that CD8+ T cells aid in tissue pathology and viral replication. Replication.[12] Studies on the CD4+ and CD8+ double-positive T cells (DP T cells) in HFRS Patients are, however, uncommon.[26] Although the clinical outcome of PUUV infection is often modest, it can nevertheless be deadly. The mortality rate is minimal, at about 0.1%. Fever, headaches, vision abnormalities, nausea, Backaches and stomach discomfort are common PUUV infection symptoms. Serious Although haemorrhages are uncommon, approximately one-third of patients experience moderate bleeding. bleeding symptoms such as conjunctival bleeding, petechiae, or epistaxis Typical symptoms of PUUV infection includes transient acute kidney damage (AKI), thrombocytopenia, and increased vascular permeability, resulting in capillary leakage. In acute HFRS, increased platelet consumption is a key mechanism producing thrombocytopenia. intravascular coagulation, increased thrombin production, fibrinolysis, and platelet activation have all been seen. Additionally, elevated blood thrombopoietin levels, immature platelet fraction (IPF%), and mean platelet volume (MPV).[27]

The detection of IgM or low-avidity IgG, both of which target the nucleocapsid (N) protein, provides the basis for the serodiagnosis of acute PUUV infection.[17] The enzyme immunoassay (EIA), immunoblotting, and immunofluorescence test (IFA) are further described in serodiagnostic methods.[40] Hantaviruses are thought to spread to people by rodent bites, ingestion of aerosolized virus from Direct contact with harmed skin or mucous membranes, as well as rodent excrement.[46]

MOLECULAR FEATURES

Hantaviruses are viruses with ribonucleic acid (RNA) surfaces. It belongs to the Bunyaviridae family. Three single-stranded, negative RNAs make up the genome, and they all share the sequence at the end of the 3′ genome segment. Hantaviruses are round, RNA viruses

that vary in size from 80 to 120 nm and contain N proteins. A bilayer of external lipids built from Golgi membranes envelopes it. Viral proteins are embedded into the top layer of the lipid bilayer, which has a thickness of 5 nm. Spikes that rise out of the surface to a depth of about 10 mm line the inside of it. It consists of two virally encoded glycoproteins, Gn and Gc, which bind oligomers in higher order and appear as protrusions and spikes on the virion's outer surface. The virion's macromolecules are composed of more than 50% protein, 20–30% lipid, 7% carbohydrate, and 2% RNA. This feature is critical for hantavirus transmission, as opposed to other bunyavirus transmission (Kallio et al. 2006).By dissolving the viral shell with lipid solvents or nonionic detergents, hantaviruses can be efficiently inactivated. the negative sense Three parts of the RNA genome are identified as small (S), medium (M), and large (L). The S segment is between 1,700 and 2,100 nucleotides long (nt). It specifies the 428–436 amino acids (aa) in the N protein that hantaviruses need to build their nucleocapsid.

The 1,150-aa glycoprotein precursor's 1,700-nt envelope is encoded by the M segment's 3,700-nt length (GPC). The cellular signal peptidase complex co-translates it into the structural glycoproteinsGn (652 aa) and Gc by cleaving it at the conserved pentapeptide motif "WAASA" at the amino terminus sequence (488 aa). It was formerly known as G1 and G2 due to a co-translational proteolytic mechanism in the endoplasmic reticulum (Löber et al. 2001). RNA-dependent polymerase is encoded by segment L, which is the biggest and is 6,500 nt in length. The protein encoded by this serves as the viral transcriptase and replicator and is designated as INTERNATIONAL JOURNAL OF ENVIRONMENTAL HEALTH RESEARCH L. Genomic negative-sense RNA is converted into messenger RNA (mRNA), which can then be translated into proteins.[7] Three ribonucleoproteins (RNPs) are produced when nonionic detergents are used to treat HTNV. These RNPs sediment to densities of 1.18 and 1.25 g/cm3 in sucrose and CsCl, respectively. One viral RNA segment complexed with the N protein makes up each of the RNP structures seen inside the virion (82, 311). Generally speaking, it is believed that each genomic RNA in the Bunyaviridae family produces a circular molecule by base pairing between inverted complementary sequences at the 3′ and 5′ ends of linear viral RNA. Since hantaviruses are devoid of a matrix protein, the N protein may fill this role to promote physical interactions with the RNPs and the glycoprotein projections on the inner leaf of the lipid membrane. According to ultrastructural research on HTNV, the virion's surface structure is made up of a grid-like pattern that is different from that of other genera in the family Bunyaviridae. The outer surface's grid-like pattern reflects the glycoprotein projections, which protrude around 12 nm from the lipid bilayer. These projections are formed of heterodimers of Gn and Gc, according to biochemical research.:

The M segment of the hantavirus codes for the surface glycoproteins G1 and G2, whichare produced as the polyprote in precursor GPC. During translocation to the ER, a cellular proteasecleaves GPC, producing mature G1 and G2 glycoproteins. Structure and properties of N protein hanta virus: The N protein of the hantavirus has around 433amino acid residues (about 50 kDa in size). Various hantaviruses appear to share a lot of the Nprotein. Large levels of N protein are evident early on following infection, according to research. Additionally, it has been shown that the early immune response in people with hantavirus is mostly focused towards N protein. As a result, a lot of viral diagnostics rely on finding the Hantavirus Nprotein or an anti-N protein antibody. The cytoplasm of the infected cell is the only place where the N protein is expressed. Since it is necessary for encasing viral RNA and controls virus replication and assembly, the hantavirus N\protein is crucial to the virus life cycle.[55]

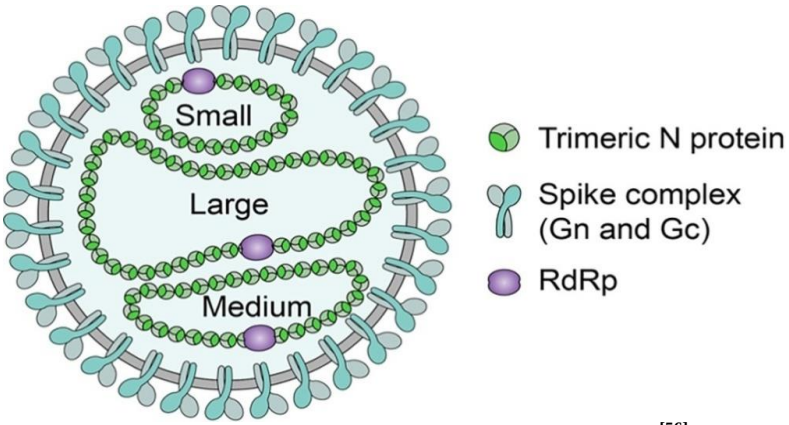

Figure No:1- Molecular structure of Hanta virus.[56]

Replication of hanta virus

Transcription and reproduction are both involved in the hantavirus genome creation of viral RNAs. transcription aids in the production of viral chromosomal RNA and protein-encoding mRNAs. All of these tasks are carried out by (RdRp) the RNA-dependent RNA polymerase of viruses. Hantaviruses are believed to enter cells through specific target cell surface proteins. Pathogens are first

attached to the target cell surface receptor to begin the reproduction cycle. In order to facilitate binding, viral Gn protein engages with integrin receptors on the exterior of host cells.α-chain and βchain make up the heterodimeric protein family known as integrins. Both cell-cell andcell-extracellular matrix binding are encouraged by it.Through the cell surface protein αVβ3 integrin and endocytosis, pathogens are able to infiltraterecipient cells. It has been demonstrated that non-pathogenic hantaviruses can attach to α5β1integrins and penetrate host cells. The virion sheath joins the endosome membrane in a pH-dependent way. The cytoplasm is where the nucleocapsids are produced.

The reproduction of viral RNA genome segments and the transcription of viral genes are then regulated by viral RNA-dependent RNA polymerase.Virons are ultimately transported to lysosomes following binding and cell entrance via clathrin-coated pits. Within the endolysosomal compartment, virionsuncoat, and three viral capsidsaredischarged into the cytoplasm. Aclathrin-coated vesicle (CCV), composed of clathrin-coated cellular membrane, is able to take upthe virus as a result. Three mRNAs are created by RdRp, one from the S, M, and L sections of the viralRNA. RdRp starts transcription. On open ribosomes, the mRNAs from S and L are translated. Thoughthe rough endoplasmic reticulum serves as the site of translation for M-specific mRNAs (ER).Twoglycoproteins, Gn and Gc, are produced when the glycoprotein precursor is intrinsically split at ahighly conserved amino acid pattern. The Golgi complex receives the glycoproteinsGn and Gcforglycosylation. The Golgi complex receives Gn and Gc, after glycosylation in the ER.

The Golgi complexis where hanta virions are thought to originate by budding into the golgicisternae then move to theplasma membrane of secretory vesicle, and exocytosis. On the other hand, New World hantaviruses do not require CCVs and reach the circulation throughthe airways. This evidence suggests that hantaviruses, like other bunyaviruses, infiltrate cells via avariety of different pathways. The caveola, clathrin-independent endocytosis-mediated receptor, macropinocytosis, and cholesterol-dependent endocytosis route are additional possible routes.[7]

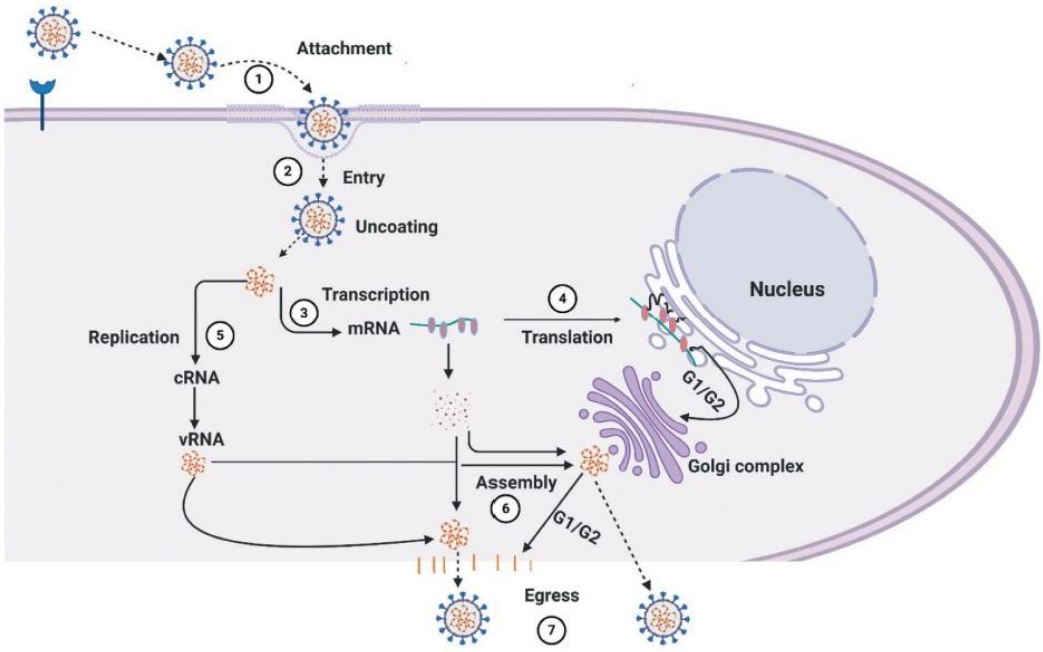

Figure No: 2 - Replication cycle of Hanta virus.[7]

PATHOLOGY

Pulmonary swelling is the most common symptom, which is then followed by respiratory failure, hypotension, and cardiogenic shock. Gn and Gc surface glycoproteins engage with target endothelial cells, macrophages, and platelets that have 3 integrin receptors at the cell membrane to cause immunological stimulation and the onset of hantaviral infection in the lungs (115). The etiology of respiratory failure and serious HPS may involve immune activation, particularly by macrophages and CD8 T cells. Proinflammatory mediators like tumour necrosis factor alpha (TNF-), interleukin-1 (IL-1), and IL-6 are released by activated macrophages. The aetiology of HPS is likely influenced by an overabundance of cytokines generated by macrophages and activated hantavirus-specific T cells in response to antigen detection on infected pulmonary endothelial cells. CD4 T helper 1 (Th1) and Th2 cells are at least two groups of helper cells that T cells differentiate after antigen detection. Gamma interferon (IFN-gamma) and TNF-gamma (or lymphotoxin-gamma) are produced by Th1 cells, which are in charge of cell-mediated defence. IL-12 controls this development. IL-4 and IL-5 are

produced by Th2 cells, which support humoral and allergy reactions.[52]

Clinical picture of hanta virus infection

An example of the dynamics of hantavirus spread demonstrating the development of the human illness. Hemorrhagic fever with renal syndrome (HFRS) typically progresses through the following five stages: feverish, hypotensive, oliguric, polyuric, and recovered. As the sickness worsens and the viral load rises, as well as when the first clinical symptoms show up, the antibodies rise. Cardiopulmonary symptoms due to hantavirus. The clinical course of HCPS is divided into prodromal, cardiopulmonary, and convalescent phases, and clinical signs can vary from mild hypoxia to breathing failure with cardiovascular shock. Theprodromal phase is usually a short, non-specific illness with flu-like symptoms like a high fever, chills, myalgia, nausea, headache, vomiting, stomach pain, and diarrhea. After that, something happens quickly respiratory interval with abrupt onset.[57]

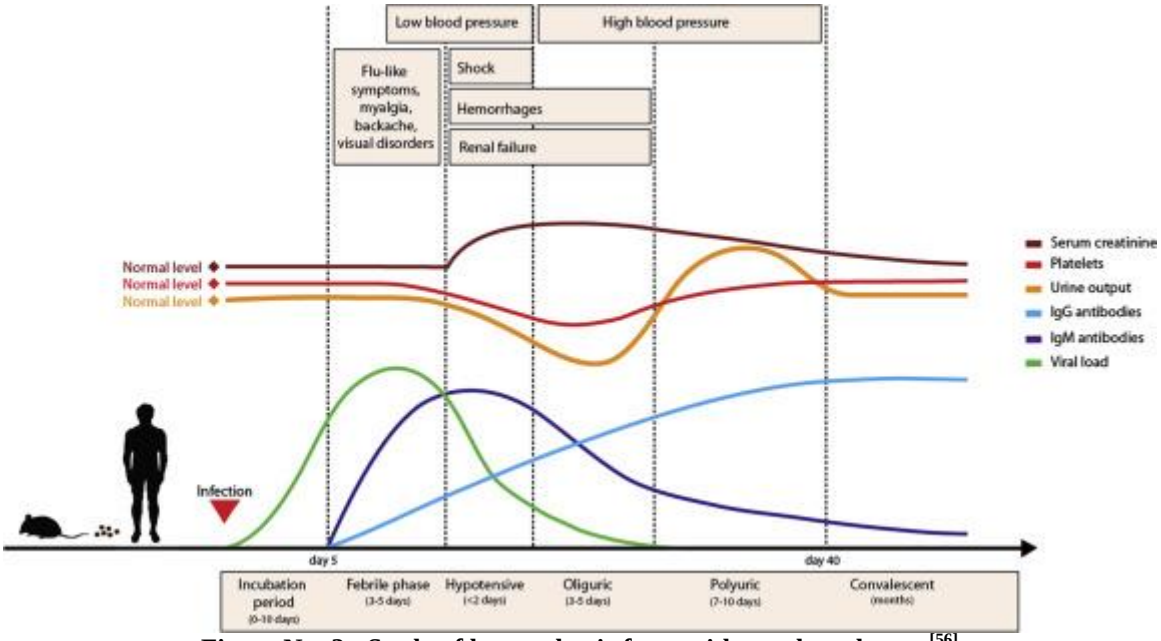

Figure No: 3 - Study of hemorrhagic fever with renal syndrome.[56]

DIAGNOSIS

An contact experience to rodents could be beneficial. Typically, the tale involves tidying a cluttered cupboard or outbuilding and coming across serious quantities of rodents or mouse excrement (Armstrong et al., 1995). Sadly, this kind of background is frequently lacking. Since all patients have experienced the prodrome, the prodrome should at least be partially present in the clinical diagnostic, along with either signs of pulmonary edoema or the aforementioned usual haematological alterations. A lobar spread or symptoms absent from the typical prodrome should cause the doctor to think about causes other than Sin name virus infection. A full blood count, including platelets, a peripheral swab to check for immature neutrophil precursors and immunoblasts, serum LDH, AST, and albumin levels, coagulation studies, a chest scan, and more should be part of the initial screening. and either an arterial blood gases or an oxygen level Patients with pneumonic plague have a condition that resembles HPS and have been brought for evaluation and possible HPS therapy. Antibodies to Sin nombre viral antigens in serum or the HANTAVIRUS PULMONARY SYNDROME 649 RT-PCR discovery of Sin nombre genetic material in blood mononuclear cell preparations are used to corroborate the diagnosis of HPS.[53]

Early detection of the Hantavirus infection nephropathy outbreak greatly decreased hospitalisation and improper antibiotic use. The majority of patients went to their primary care physician first, showing that general practitioners are frontline medical professionals during epidemics. Oligo- and polyuria (82% vs. 97%), fever, and exhaustion are thought to be the primary symptoms of NE, per research done in secondary care. In our investigation, general practitioners were able to record a variety of clinical images with lower frequency of oligo- and polyuria (21% vs. 31%). This might be attributed to general practitioners seeing somewhat milder instances, to early exams with non-fulminantsymptomatology, or it could just be a bias resulting from the retrospective research design. The need of improved diagnostic tools and protocols is reinforced by the fact that 38% of patients required hospitalisation, which was dramatically reduced when patients received the proper diagnosis at the first visit.[54]

TREATMENT

1. Emergency Department and Pre-Intensive Care Unit
2. Intensive Care Unit Management
3. Salvage Therapy
4. Isolation Precautions

Emergency Department and Pre-Intensive Care Unit:
Patients with suspected HPS should be moved right away to a centre with experience and knowledge in handling severe shock due to the illness's excessive severity and how quickly it advances. Prior to transport, large-bore catheter intravenous access should be obtained. Patients with hypotension should be given crystalloid or colloidal drinks. Agents with primarily vasoconstrictor effects should be avoided.[53]

Intensive Care Unit Management
Patients who experience a significant pulmonary capillary leak also experience myocardial insufficiency and shock, which need for higher heart filling pressures. Fluid streams randomly into the alveolar space during volume delivery when pulmonary capillary pressures rise. Pressures of pulmonary artery blockageKnowing that blood pressures greater than 10 to 12 mm Hg cause significant flooding of the alveolar area with edoema fluid must temper the impulse to give volume to a patient who could be hypotensive. The administration of an inotropic drug to patients should occur concurrently with volume resuscitation.[53]

Salvage Therapy :
Due to the lung capillary rupture and cardiogenic shock, which appeared toIt was suggested that ECMO might be a suitable treatment for some patients with HPS since the method could handle both issues concurrently and resolve rapidly in recovering patients (Crowley et al., 1998). The scientists also hypothesised that because of the quick recovery of the survivors, the length of ECMO would be shorter than had been seen in patients with ARDS, lowering the risk of nosocomial sepsis. For some seriously sick HPS patients who would otherwise pass away, ECMO seems to be a workable form of salvage treatment. Nitric oxide inhalation has also been used to help one patient with serious HPS.[53]

Isolation Precautions:
There is no proof that the Sin nombre virus can transmit from person to person; rat exposure is a sufficient explanation for every instance in North America. 266 healthcare professionals who had different levels of contact to HPS patients or to their blood and bodily secretions participated in a research of nosocomial transmission during the 1993 Four Corners epidemic. By using molecular epidemiological methods, it may be possible to rule out the chance of respiratory transfer from person to person. With this method, it would be possible to collect viral samples from each affected patient and identify the RNA patterns of each patient's virus. Viruses from geographical areas separated by more than 100 metres should have small base changes (substitutions), even though the sequences of all viruses within a genus are essentially similar.[53]

There are currently no antiviral medications that have been licenced by the US Food and Drug Administration for use against HFRS or HPS. As a result, only supportive care is used in themanagement of severe cases. In these individuals, maintaining fluid and electrolyte balance iscrucial. Serious renal failure in HFRS patients may necessitate extracorporeal blood purification(dialysis treatment). Mechanical breathing or extracorporeal membraneoxygenation could benecessary in HCPS. In addition to supportive treatment, immune therapies and antiviral medicationsfor HFRS and HPS have been tested. These are what they are:Ribavirin-For HPS patients who had advanced to the cardiopulmonary phase, ribavirin wasineffective.Favipiravir-suppresses SNV and ANDV effectively. Lactoferrin-the suppression of virus adsorption to cells by lactoferrin antiviral action against theHantavirusVandetanib-inhibiting the activation of VEGF-receptor 2 with a tyrosine kinase inhibitor.[58]

PREVENTION

The risk category for hantavirus infection includes those who come into touch with rats or theirexcrement. Therefore, the most crucial stage in the disease & prevention is rodent control in homesand other places where there are human activities taking place. First-generation vaccines- In places where HFRS is extremely prevalent, HTNV and SEOV inactivatedvaccines have been utilised since 1995. For HFRS, the formalin-inactivated HANTA vaccine Hanatvirus been extensively utilised. Second-generation vaccines-vaccination with virus-like particles, Dihydrofolatereductase was co-transfected with a vector harbouring the HTNV M segment and CD40L/GM-CSF gene to create HTNVvirus-like particles (VLPs) adorned with CD40L or GM-CSF.

Third-generation vaccines- vaccination using recombinant vector Animals susceptibility tohantavirus infection can be prevented using recombinant vector vaccinations According to the vaccine delivery technology, two (phase I) clinical studies were performed toevaluate the efficacy and safety of HTNV and PUUV M segment DNA viruses. In both studies, vaccines were deemed safe with no significant negative effects for use in humans. Targeting the HTNV Gn or HTNV Gc combined with lysosome-associated membrane protein 1, two distinct DNAvaccines were created. (LAMP1). Strong humoral, cytoplasmic, and long-lasting immune responsesare produced when CD4+ T cells are stimulated and the antigen-presenting pathway is altered byLAMP 1. Long-lasting immune reactions in vivo were shown for both immunizations.[58]

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