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OVERVIEW ON HANTAVIRUS CARDIOPULMONARY SYNDROME: IS IT THREATENED TO ARAB COUNTRIES INCLUDING EGYPT?

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Abstract

Orthohantavirus is a genus of single-stranded, enveloped, negative-sense RNA viruses in the family Hantaviridae within the order Bunyavirales. Members are called orthohantaviruses or simply hantaviruses. Hantavirus pulmonary syndrome (HPS), Hantavirus is a life-threatening zoonotic disease characterized by pulmonary edema, hypoxia, and hypotension, started by vague flu-like symptoms or can involve hemorrhagic fever and renal syndrome (HFRS). Hantaviruses are transmitted by contact with the bodily fluids of rodents, particularly from saliva from bites and especially from inhalation of viral particles from urine and feces in aerosols. Among the HCPS-causing hantaviruses is the *Andes orthohantavirus*, the only hantavirus confirmed to be capable of spreading from person to person, though this is rare!!! Generally speaking, the virus diseases are a continued threat to human health in both community and healthcare settings worldwide.

Key words: Hantavirus, Cardiopulmonary syndrome, Renal syndrome, Pathogenicity, Risks

Introduction

Of more than 20 known species of rodent-borne viruses within the genus Hantavirus, family Bunyaviridae; 11 cause human disease (Schmaljohn and Hjelle, 1997). Hantavirus diseases are recognized two major forms: the hemorrhagic fever with renal syndrome (HFRS) and Hantavirus cardiopulmonary syndrome (HCPS or HPS). Among HCPS agents, the most severe forms are associated with Sin Nombre virus (SNV) and the southern (prototypical) form of Andes virus; slightly milder forms are caused by the northern form of Andes virus (Andes-Nort), Laguna Negra virus (LNV), and Choclo virus (Mertz *et al,* 1997). In general, case-fatality ratios of HCPS range from 30 to 50% for severe forms and 10 to 30% for milder forms. The illness caused by Choclo virus (Panama) is the mildest form of HPS, when nearly always or always lacks a significant component of cardiac insufficiency and has a markedly lower case-fatality ratio (CDC, 1993). Kanerva *et al.* (1998) in Finland found asymptomatic Hantaviruses were rodent/insectivoborne negative-stranded RNA viruses. But in humans were agents of hemorrhagic fever with renal syndrome (HFRS) & Hantavirus pulmonary syndrome (HPS), both with a significant mortality. In cell culture Hantaviruses didn't cause cytopathic effects and mechanisms of diseases in man were not well known. Increased capillary permeability was a central fact in its pathogenesis. Although viruses have *in-vivo* a predilection for endothelial cells, and those inflammatory mediators of host immune response played a significant role in capillary leak producing abrupt hypo-tension and shock in severely illness. Mediators released by activated macrophages including important NO & TNF-α, and HFRS renal failure pathogenesis must be resolved. Martens (2000) in Germany examined 694 sera obtained from 1994 to1998 from general population with a recombinant enzyme immunoassay for hantavirus antibodies against serotypes Hantaan and Puumala, and positive ones were confirmed with an

indirect immuno-fluorescence assay & a recombinant immunoblot. Antibody prevalence of 0.9% signified that Mecklenburg-Vorpommern was not an endemic area, as 12/196 patients had strong cross-reactivity in Hantaan group and only one patient developed HPS. All professional high risk worke-to scientific studies that were initiated after the Korean War (1951-1953), during which >3000 Korean hemorrhagic fever cases were detected among the UN troops (Jiang *et al,* 2017). In May 1993, clinicians working with the Indian Health Service in Four Corners region of the southwestern USA noted many cases with severe respiratory illness affected the previously healthy youths. Syndrome was characterized by a nonspecific prodrome, followed by rapid development of non-cardiogenic pulmonary edema and hemodynamic compromise with high death rates (Jenison *et al,* 1995).

A rapid response to the newly described syndrome was initiated by the Indian Health Service, University of New Mexico, School of Medicine, State Health Officials, & CDC. Sera from patients proved to be broadly reactive to conserved viruses regions of genus Hanta-virus (Lee *et al,* 1978). Members of this genus previously were identified as the etiologic agents of hemorrhagic fever with renal syndrome (HFRS), which occurred principally in Europe and Asia (Niklasson and Le Duc, 1984).

Rodent reservoirs: An extensive rodent trapping campaign was initiated, based upon an early case-control study that identified contact with rodents as the principal risk factor for illness in Four Corners outbreaks and that a rodent reservoir was responsible for HFRS transmission (Zeitz *et al,* 1995). An outbreak of Hantavirus pulmonary syndrome (HPS) was in the southwestern USA identified an unusually large numbers of deer mice (*Peromyscus maniculatus*) with Hantavirus virus by RT-PCR (Jonsson *et al,* 2010). The genetic characterization of a new member of genus Hantavirus was termed Sin Nombre virus (SNV), followed these develrs to Hantavirus infection didn't show increased antibody. Dialysis patients had antibody prevalence as general population.

Review and Discussion

Historical perspective: The virus was named as Hantaan virus, after the name of the Hantan River, which discovery dated back opments (Zaki *et al,* 1996), and illness was named Hantavirus cardiopulmonary syndrome (HCPS). It became clear that HCPS predated the Four Corners outbreaks, with retrospective diagnoses being made for cases occurred in 1959 (Khan *et al,* 1996). HCPS was due to SNV or closely related viruses occurred throughout North and South America. Between 1993, when HCPS was identified in the USA, and December 2010, 560 confirmed cases were reported from 32 states, the majority of which were in the southwestern United States (CDC, 2011). Cases have also been identified in Canada and Central and South America (Mertz *et al,* 2006). But, Padula *et al.* (1998) and Martinez *et al.* (2005) in the South American HPS outbreaks included two confirmed and one suspected epidemic with human-to-human transmission, which highlighted the potential for Hantaviruses to evolve from a spillover zoonosis into an emerging human pathogen. Schmal-john *et al.* (1996) reported that Hantaviruses were single-stranded negative-sense RNA viruses whose genome consisted of three segments, which were designated Small (S), Medium (M), and Large (L) and co\de for the nucleocapsid, the two envelope glycoproteins (G1& G2), and RNA-dependent RNA polymerase, respectively. Hughes and Friedman (2000) by phylogenetic analyses of S, M, & L genes of Hantaviruses (Bunyaviridae: Hantavirus) showed three well-differentiated clades corresponding to viruses parasitic on three rodents of family Muridae subfamilies (Murinae, Arvicolinae, and Sigmodontinae). In rooted trees of M & L genes, viruses with hosts of Murine formed an out-group to those with hosts in Arvicolinae and Sigmodontinae, but rather Hantavirus was transmitted directly or indirectly

between hosts during aggressive interactions or via inhalation of infectious aerosols released in urine and feces (Plyusnin and Morzunov, 2001). However, the infected rodents suffered from decreased survivorship, particularly during winter (Kallio *et al,* 2007). However, Hantaviruses are highly pathogenic in man, in Old World cause hemorrhagic fever with renal syndrome (HFRS) with mortality rates up to 15%, and in the New World viruses resulted in hantavirus pulmonary syndrome (HPS) with epidemic fatality rates up to 50% (Zeier e*t al,* 2005). Comparisons of Hantavirus phylogeny with that of Muridae rodents, infection showed strong topological correspondence between them and that the patterns of amino acid replacement in viruses were also compatible with a history of host-specific adaptation (Ramsden *et al,* 2009). Switching between closely related hosts was widely occurred in Hantaviruses and could contribute to a cophylogenetic pattern that resembles codivergence (de Vienne *et al,* 2007).

Eckerle *et al.* (2014) in Germany reported that reservoir host species were increasingly recognized besides representatives of order Rodentia, included other mammalian orders Soricomorpha/Eulipotyphla and Chiroptera. Despite the great interest created by emerging zoonotic viruses, there was still a gross lack of *in-vitro* models to reflect exclusive host adaptation of most viral zoonosis. They added that well-characterized reservoir cell lines covering a wide range of bat, insectivore and rodent species were essential. They concluded the established approaches to generate reservoir-derived cell culture models for *in-vitro* study of virus-host interactions, using model systems almost exclusively originate from bats and bat-borne viruses other than Hantaviruses. They proposed a parallel approach for research on rodent-and insectivore-borne Hantaviruses, taking the generation of novel rodent and insectivore cell lines from wildlife species would be also valuable for rodent-borne viruses, as orthopox- and arenaviruses.

Epidemiology: Hantavirus infections were reported from all continents except Australia population who carried only antibodies (Bi *et al,* 2005). Regions especially affected by the HFRS include China, the Korean Peninsula, Russia (Hantaan, Puumala, and Seoul viruses), and Northern and Western Europe (Puumala and Dobrava virus). Regions with the highest incidences of Hantavirus pulmonary syndrome were in Argentina, Chile, Brazil, USA, Canada, and Panama (Anthony, 2020), and Africa (Klempa *et al,* 2012)

Ulrich *et al.* (2004) in Berlin reported that pathogenic European Hantaviruses caused a human hemorrhagic fever with renal syndrome of various severities, as diagnosis by immuno-fluorescence assays using virus-infected cells or enzyme immunoassays and Western blot tests using recombinant nucleocapsid proteins. In German professionally exposed risk groups (as forest workers) seroprevalence was higher than that in the normal ones (1%). Endemic Hantavirus infections regions were mainly in Baden-Württemberg, as in years 2001-2003 an annual number of about 200 clinically apparent Hantavirus infections were reported. They added that neutralization assays detected almost exclusively human infections caused by Puumala and Dobrava viruses, only very rarely by Tula virus. Besides, infections caused by German Hantaviruses were up to 10% of clinically Hantavirus infections were caused by introduced patients from other countries, mainly Europe. But, so far only very limited molecular genetic Germany data about the circulating Hantaviruses were available

Larbig *et al.* (2013) in German reported a 40 year old, disoriented, HIV- and Hepatitis B positive male patient was admitted with 40.3°C, a sinus-tachycardia (160/min) and hypotension (70/60mmHg). Laboratory tests showed elevated parameters, azotemia, proteinuria and thrombopenia, CD (4+) T-helper cells: 320/µl (32%), HIV RNA: <40copies/ml, HBV/DNA: 20800copies/ml. Hantavirus immunofluorescence antibody assay1:2048; serotype Puumala. Patient was a goal-direc-

ted therapy and Piperacillin and Tazobactam antibiotic was initiated. He developed a bipulmonal infiltrate and an ARDS required tracheal intubation and a triad of fever, renal failure and profound hemorrhagic symptomms led to diagnose Puumala infection, as parallel HIV & HBV an antiretroviral therapy was initiated. They concluded that Puumala virus has potential for a severe multiorgan failure that was not typical for this usually benign infection. Tassart *et al.* (2014) in Belgium Puumala Orthohantavirus (PUUV), an Orthohantavirus species reported a 62years old man who developed Guillain-Barré syndrome (GBS) post Hantavirus infection. Progressive GBS caused symmetrical weakness of lower limbs extended to upper limbs and face and low or absent tendon reflexes that was a potentially life threatening disorder and needed timely treatment to ensure fast recovery with mild complications.

Vollmar *et al.* (2016) in Germany found that Puumala virus (PUUV) caused the mild HFRS in the predominating endemic Hantavirus, and reported a severe case of a PUUV infection in summer 2015 in South Eastern region PUUV known endemic >10 years. A 54-year-old female gardener was hospitalized with fever, cough and dyspnea. Within 48 hrs he developed a rapid progressive ARDS with circulatory failure and required ECMO (extracorporeal membrane oxygenation) treatment. Serological and molecular biology confirmed the PUUV infection with partial sequences of S- & M-segments clustered to a strain previously known in South Eastern Germany. They reported case highlighted rare incidents PUUV caused Hantavirus cardiopulmonary syndrome, usually found after infections with New World Hantaviruses, and neurological symptoms.

Vetter *et al.* (2019) reported 3 cases of Puumala virus infection in a Switzerland family, with clinical pictures ranged from mild influenza-like illness to fatality. They concluded that the cluster illustrated the wide range of clinical manifestations of Old World Hantavirus infections and diagnosis challenge travel-related hemorrhagic fevers. Koskela *et al.* (2021) in Finland reported that Puumala Hantavirus (PUUV) causes a hemorrhagic fever with renal syndrome (HFRS), or called nephropathia epidemica (NE) mainly endemic in Europe and Russia. Clinical features include a low platelet count, altered coagulation, endothelial activation, and acute kidney injury. Multiple connections between coagulation pathways and inflammatory mediators, as well as complement and kallikreinkinin systems were reported, with usually mild bleeding symptoms. They also have an increased risk for disseminated intravascular coagulation (DIC) and thrombosis.

Clinical case definition: The CDC (2006). defined a clinical case of HCPS as follows: a febrile illness (e.g., temperature greater than 101ºF (38.3ºC) characterized by bilateral diffuse interstitial edema that may radiographically resemble adult respiratory distress syndrome (ARDS), with respiratory compromise requiring supplemental oxygen developing within 72hrs of hospitalization, and occurring in a previously healthy person. Alternatively, a case can be defined as an unexplained respiratory illness resulting in death, with an autopsy examination demonstrating non-cardiogenic pulmonary edema without an identifiable cause. These case definitions were not diagnostic of HCPS, but were chosen to be inclusive (Vincent *et al,* 2000). The US Public Health Service's national database requires virus-specific laboratory confirmation before reporting a case as HCPS.

Clinical features: Patients with HPS typically present in a very nonspecific way with a relatively short febrile prodrome lasting 3-5 days, but fever and myalgias, early symptoms include headache, chills, dizziness, nonproductive cough, nausea, vomiting & other gastrointestinal symptoms. Malaise, dia-rrhea, and lightheadedness were reported by 50% of all patients, with less frequent reported of arthralgias, back pain, and abdominal pain. Patients may report shortness of breath, (respiratory rate usually 26-30times/minute). Typical findings on initial presentation

included fever, tachypnea and tachycardia, but physical examination was usually otherwise normal. Most frequent was fever, chills, and myalgias, but frequent was headaches, nausea, vomiting, abdominal pain, diarrhea, cough, & malaise. Others were shortenss of breath, dizziness, arthralgia, back or chest pain, & sweats. At this stage, as cough and tachypnea generally do not develop until about day seven. Once cardiopulmonary phase begins, however, the disease progresses rapidly, necessitating hospitalization and often ventilation within 24hrs. Signs that make a diagnosis of HPS unlikely include rashes, conjunctival or other hemorrhages, throat or conjunctival erythema, petechiae, and peripheral or periorbital edema (CDC, 2012).

Incubation period: Typically a period of 2 to 3 weeks elapses between exposure to a Hantavirus and first symptoms. Isolated cases with shorter or longer incubation periods were reported. A total of 11 Hantavirus patients had well-defined and isolated exposure to rodents; the median incubation period was 14 to 17 days, with range 9 to 33 days (Young *et al,* 2000). However, in a case that was reported subsequently, the estimated incubation period was about seven weeks (Fritz and Young, 2001). Virus replication may be localized to a body surface or, alternatively, and become generalized or systemic following spread from entry sites via lymphatic and hematogenous routes. Example testis infection or accessory sexual organs may lead to excretion of virus in the semen and the risk of transmission during sexual activities. In some cases of hemorrhagic fever, virus continues to be shed in the semen long into convalescence. Virus localized in the salivary glands (e.g., in mumps), mammary glands, kidney tubules, and lungs led to excretion in the saliva, milk, urine, and respiratory secretions. Most viral infections of the mother have no harmful effect on the fetus, but some blood-borne viruses cross the placenta to enter the fetal circulation, sometimes after establishing infection foci in the placenta. Severe cytolytic infections of fetus cause fetal death and abortion, a pattern common in smallpox (Burrell *et al,* 2017). Fetal death and nearly universal death of a mother was in Ebola, Marburg, and Lassa hemorrhagic fevers. Fetal teratogen resulted after rubella and cytomegalovirus infections during pregnancy (Morsy *et al,* 2022)

Prodrome/febrile phase: The earliest clinical manifestations of HCPS consist of fever, chills and myalgias, which can be severe in many cases. At this stage, HCPS is difficult to distinguish from other viral syndromes. However, an experienced clinician often suspects HCPS during the prodromal phase of illness because the constellation of clinical findings and setting (e.g., likely rodent exposures) are characteristic of HCPS but not of other illnesses. During 2 to 8 days phase, the disease increases in severity at a rapid pace, often leading to nausea, vomiting, weakness, sometimes diarrhea, and headaches prominent. Abdominal pain can be significant enough to mislead the clinician into diagnosing of acute abdomen.

Classic features of upper respiratory tract disease (URI) such as rhinorrhea, pharyngitis, coryza, and ear pain were absent in most patients with Hantavirus diseases, except for cough, but, pharyngitis is sometimes occured in HCPS children (Saikku, 1997).

Some HCPS forms (Andes-HCPS) can present with conjunctivitis, facial flushing and varying numbers of fine petechial on the trunk, axillary folds, soft palate, or neck.

The prodromal phase is followed by the rapid onset of hypotension and non-cardiogenic pulmonary edema, as given below.

Cardiopulmonary phase: The cardiorespiratory or cardiopulmonary phase denotes the point at which capillary leak into the pulmonary bed occurs. This phase can last from two to more than seven days depending upon the overall infection severity (Lee and van der Groen, 1989). A dry cough often heralds the abrupt transition to cardiopulmonary phase (Castillo *et al,* 2001). The rapidity with which the features of the prodromal phase progress to shock, coagulopathy (with

hemorrhage common due to Andes virus), pulmonary edema, bronchorrhea, arrhythmias, and death have led experienced clinicians to triage patients with hantavirus infection to a tertiary care center at the earliest possible stage of disease (Crowley *et al,* 1998). Once the first signs of cardiopulmonary involvement are apparent, it is not uncommon for the local clinician to be caught in the difficult bind of attempting to transport a critically ill patient to a tertiary care center hours away (Koster and Hjelle, 2002).

Oliguric and diuretic phases: Separate phases characterized by oliguria (3 to7 days), then diuresis of variable length reported for HFRS, but are emphasized less in clinical descriptions of HCPS (Passaro *et al,* 2001).

Convalescent phase: The resolution of the cardiorespiratory phase of HCPS occurred as quickly and dramatically as an onset, over periods as short as 24 to 48hrs, but complete recovery from severe HCPS was a slow process (Levy and Simpson, 1994).

Laboratory results: Hantavirus earliest and among the more specific laboratory abnormalities is a rapid decline in the platelet count; this occurs as early as prodromal phase of illness. Others, but less specific abnormalities were an increase in serum LDH levels, which occurs early, and elevations in hepatocellular enzymes and lactate, which occur later (Chandy and Mathai, 2017).

Immunoblasts, resembling those observed in the lungs and lymphoid tissues of patients with HCPS, become abundant in blood in advanced cases from the prodromal into the cardio-respiratory stage of illness. This was concomitant with the appearance of markedly left shifted cells of the granulocytic series. While the decrease in platelet count appeared early in the illness course, thrombocytopenia didn't reliably distinguish those who develop the most severe disease forms from those experienced a less severe disease course (Koster *et al,* 2001). By contrast, leukocytosis (up to 90.000cells/microL) and the appearance of immuno-blasts are more pronounced in the patients with severe illness forms. Simultaneous appearance of thrombocytopenia, a left-shifted granulocytic series, and an immunoblast count that exceeds 10% of total lymphoid series was diagnostic triad, which sufficiently diagnosis when used at substantial experience centers with HCPS to triage patients for extracorporeal membrane oxygenation (ECMO) and other specialized tertiary care. A decrease in the serum concentration of albumin occurs concomitantly with increases in blood hemoglobin and hematocrit. Abnormalities were markers for capillary leak severity. Increases in partial thromboplastin time and prothrombin time seen in more severe Hantavirus infection.

Radiologic results: HPS begins with minimal changes of interstitial pulmonary edema, progress to alveolar edema with severe bilateral involvement. Pleural effusions were common and often large enough to be evident radiographic. Heart size is usually normal. Cardiac silhouette size on chest radiographs was usually normal. A case fatality occurred when metabolic acidosis, prolongation of PT & PPT times and rising serum lactate levels develop, the prognosis is poor, with development of proteinuria, and mild elevations of transaminases, CPK, amylase, and creatinine (CDC, 2012).

Serologic results: Serology tests are the dependable diagnosis for acute or remote Hantaviruses infection. By time symptoms evidented patients uniformly have antiviral antibodies of IgM & IgG classes. ELISA, SIA, Western blot, IFA, CFT, IHAT, and focus or plaque reduction neutralization tests detected Hantaviruses antibodies, but not approved by FDA at that time (Hjelle *et al,* 1997).

Acute infection can be distinguished from remote (past) infection by the presence of specific anti-Hantavirus IgM (usually nucleocapsid or N antigen was used) or a fourfold rise in titers of anti-hantavirus IgG. In USA, those state health departments that offer Hantavirus diagnostic tests use IgG and mu-capture IgM ELISAs developed and distributed by CDC. The ELISAs use recombinant-expressed N antigen. A similar test was also

used in Canada. A Western blot assay using recombinant antigens & isotype-specific conjugates for IgM/IgG differentiation developed, which performs similarly. Western blot is largely supplanted by the SIA. Detection of viral RNA by nested reverse transcription-polymerase chain reaction (RT-PCR) in plasma, blood cells, or tissues was diagnostic for Hantavirus infection, but tests were usually not indicated due to high diagnostic accuracy of serologic assays. Postmortem diagnosis is accomplished using an immunohistochemical test for N antigen from tissues (kidneys, lung) in paraffin blocks or viral RNA by RT-PCR (Nunes *et al,* 2019).

When to suspect Hantavirus: HCPS should be suspected in settings in which a patient from a rural area or with potential exposure to wild rodents presents with fever, chills, and myalgias, especially in the presence of nausea and vomiting. Specific serologic diagnosis should be considered in patients with thrombocytopenia, leukocytosis, bilateral interstitial in-filtrates, or elevated LDH.

It is a must to obtain a CBC if Hantavirus disease was suspected, because thrombocytopenia and/or leukocytosis or leukopenia detected at the first or second blood examination (Chapman *et al,* 2002). But, there must be a low threshold for ordering a specific serologic test, since modern antibody tests are accurate and because at least some clinical laboratories are able to complete the testing on the same day that they receive the sample (Mertz *et al,* 1999). Combination of atypical lymphocytes, a significant bandemia, & thrombocytopenia in pulmonary edema highly indicate Hantavirus infection (CDC, 2012).

Differential diagnosis: By the time pulmonary disease develops, constellation of pulmonary and/or cardiac insufficiency, bilateral interstitial infiltrates, fever, rural origin and/or rodent exposure, thrombocytopenia, leukocytosis and lymphocytic atypia, elevated lactate dehydrogenase, and transaminases are virtually pathognomonic. Differential diagnosis that one might entertain depends upon what other respiratory or septic illnesses were incident in region. Other respiratory infections must include Legionella, Chlamydia, Mycoplasma, and Q fever (Moolenaar *et al,* 1995). Depending upon geographic setting and exposure history, septicemic plague or tularemia, leptospirosis, dengue fever, or yellow fever might be entertained. Abdominal manifestations may be sufficiently severe and isolated to consider appendicitis or cholelithiasis. Non-infectious etiologies include diseases associated with pulmonary hemorrhage, such as granulomatosis with poly angiitis (Wegener's) and Goodpasture's syndrome.

Generally speaking, Hantavirus must be differentiated from Viral Hemorrhagic Fevers (El Bahnasawy *et al,* 2015), Acute Respiratory Distress Syndrome (ARDS), Mycobacterial Pneumonia, and Influenza Pneumonia (Clement *et al,* 2019)

Symptomatic treatment, supportive care, or supportive therapy is any medical therapy of a disease affecting its symptoms, not the underlying cause, but aimed at reducing the signs and symptoms for the comfort and well-being of the patient, but it also may be useful to reduce organic consequences and squeals of the signs and symptoms of disease (e.g., most viral diseases, such as influenza and Rift Valley fever), symptomatic treatment was the only available so far: 1- Analgesics, to reduce pain, 2- Anti-inflammatory agents, for arthritis inflammation, 3- Antitussives, for cough, 4- Antihistamines for allergy, 5- Antipyretics, for fever, 6- Enemas for constipation, & 7- Treatments to reduce side effects from drugs (NCI, 2011).

Dheerasekara *et al.* (2020) in Sri Lanka reported that severe HPS or HFRS case management was purely based on supportive treatments, often in an ICU. Rodent control, public health education and promotion play a major role in preventing Hantavirus infection. Zhang *et al.* (2021) in China described molecular mechanisms of Hantavirus evasion mechanisms of IFN signaling pathway and cellular processes such as regulated cell death and cell stress. Also, Hantavirus could

evade immune surveillance evasion through cellular mechanisms as up-regulating immune check-point molecules interfering with viral infections. Understanding Hantavirus's antiviral immune evasion mechanisms deepened on pathogenesis and developing more effective means to control and eliminate Hantavirus. Shkair *et al.* (2022) in Russia reported that the highest rate was among zoonotic disease cases; mostly were HFRS cases in Volga region with Puumala virus (PUUV) as a pathogen. They developed new ways for HFRS prevention by testing efficacy of microvesicles (MVs) as PUUV nucleocapsid (N) and glycoproteins (Gn/Gc) delivery vehicles. They concluded that MVs could deliver PUUV N and Gn/Gc proteins in vitro and that MVs loaded with PUUV proteins elicit a specific humoral & cellular immune response *in-vivo* that suggested an MV-based vaccine could control HFRS, unusual for patients to succumb solely from respiratory failure in centers at sophisticated ventilator support is a must (Macneil *et al,* 2011). Given the role of capillary leak in the development of noncardiogenic pulmonary edema & hypotension, early vasopressors to control hypotension and cautious use of intravenous fluids (Ellender and Skinner, 2008)

Extracorporeal membrane oxygenation: ECMO has been used successfully in many cases (Dietl *et al,* 2008). The technique has been used only in patients who were regarded as extremely likely to die from HCPS; in this subset, survival has been about 50%. At centers with significant expertise in ECMO, severely compromised cardiac output is considered an especially important factor in deciding which patients is most likely to require this specialized therapy. Patients with a cardiac index of <2.5 L/min/m2 despite attempts to resuscitate with pressors and inotropic agents were ECMO potential candidates (Shekar *et al,* 2014)

Antiviral therapy: Ribavirin is a nucleoside analogue that is effective in HFRS due to Hantaan virus, a different strain of Hantavirus (Sun *et al,* 2007). A prospective, randomized, double-blind, placebo-controlled trial of 242 patients with serologically confirmed Hantaan virus in the People's Republic of China found a sevenfold decrease in mortality among ribavirin-treated patients (Huggins *et al,* 1991). The major side effect of ribavirin was anemia, which reversed upon the therapy completion. Unfortunately, in China rural regions HTNV-HFRS was most common; few patients received intravenous ribavirin therapeutically due to high cost. However, ribavirin (as in early yellow fever treatment) at clinical-relevant doses prevented seroconversion and diminished viral replication in a deer mouse model, but was completely premature to exclude its value against SNV, such as in post-exposure prophylaxis or early infection (Sbrana *et al,* 2004).

Since ribavirin has activity against SNV in vitro, two trials examined the role of this nucleoside analogue for the treatment of HCPS were conducted. However, study design and patient enrollment was insufficient to allow its efficacy to be yes, or no. The results of an open labeled, nonrandomized trial with 30 patients from June 1993 to August 1994 did not decrease mortality with ribavirin use, and concluded that a randomized, placebo-controlled trial during the prodrome phase would be necessary to assess drug efficacy (Chapman *et al,* 1999).

An NIH-sponsored, double-blind, placebo-controlled trial to further evaluate the role of ribavirin therapy in HCPS enrolled 36 patients from 1996 to 2001; among the 23 patients with confirmed SNV infection, 10 received intravenous ribavirin and 13 received placebo (Mertz *et al,* 2004). The study was ended before the target number of subjects was enrolled due to slow accrual. Overall, 8/10 ribavirin recipients and 11/13 placebo recipients survived at day 28 of the study. Besides, there were no significant differences or trends between groups to measures shock or respiratory failure. They concluded, that although the study lacked adequate power to determine whether ribavirin was safe or effective, the lack of trends favoring its use su-

ggested that ribavirin did not have a significant role in the treatment of Hantavirus cardiopulmonary syndrome.

Based upon these observations, the use of ribavirin off protocol cannot be recommended to establish HCPS. Because of the virus's known susceptibility to ribavirin in cultured cells and in the deer mouse model, the drug might still be considered should the syndrome be recognized during an exceptionally early stage (Medina *et al,* 2007). Ribavirin may be a drug for HPS and HFRS, but its effectiveness remains unknown, spontaneous recovery is possible with supportive treatment. Hantavirus infection suspected patients may be admitted to a hospital, and given oxygen and mechanical ventilation to help breathe during the acute pulmonary stage with severe respiratory distress (CDC, 2016).

Prevention: Given the limited treatment options and high case-fatality rate of HCPS, prevention of disease is a must. Recommendations from the CDC focus on measures to limit contact with potentially infectious rodents in affected areas, particularly in indoor, poorly ventilated spaces. 1- All holes that might allow rodents to enter indoors must be sealed with steel wool, wire screen, cement or other patching material. 2- Seldom used buildings should be opened and aired out prior to entry. 3- Potential nesting sites outdoors should be eliminated by clearing brush and debris from around the foundation and elevating hay, woodpiles, and garbage cans. If nesting sites are discovered, latex gloves should be worn during clean-up, and nests must be soaked with 10 % bleach or detergent solution prior to removal to prevent aerosolization. Latex gloves should be disinfected prior to removal and hands should be washed thoroughly. 4- If heavy infestation is present in an area where HCPS was reported, it is recommended that the appropriate local, state, or federal health officials be consulted prior to clean-up (CDC, 2005)

Vaccine development: Efforts to produce vaccines for Hantaviruses have favored the products that elicit neutralizing antibodies, a preference that can be traced to early studies that showed a strong correlation between the efficacies of vaccine preparations and the titers of neutralizing antibodies they engendered (Xu *et al,* 1992). Yet, passive antibody therapy has not been actively pursued for Hantaviruses, in part because of the widespread recognition that patients exhibit potent antibody responses by the time of presentation. It is interesting to observe that evidence has accrued demonstrating that patients who present with high titers of neutralizing antibodies to SNV are those who are destined to have milder disease, whereas lower titers of neutralizing antibodies tend to occur in patients who died or required ECMO salvage therapy (Bharadwaj *et al,* 2000). Unfortunately, few vaccines are licensed or available worldwide. In China and Korea, killed-virus vaccines are available for HTNV and/or SEOV, but their expense precludes for widespread usage in the heavily-affected regions. No vaccines were available for SNV, PUUV, DOBV, LNV or Andes virus (Hooper *et al,* 2001). Liu *et al.* (2020) in China reported that now no effective treatment was available for either HFRS or HCPS. Only whole inactivated vaccines against HTNV or SEOV are licensed for use in Korea and China, but protective efficacies of these vaccines are uncertain. At present, severe HPS or HFRS case management is purely based on supportive treatments, often in an intensive care unit. Rodent control and public health education and promotion play a major role in preventing Hantavirus infection.

What about Egypt? Botros *et al.* (2004) in Cairo reported a hospital-based case-control study in February 1998, to diagnose Hantavirus among chronic renal disease (CRD). Patients were 350 with a CRF history and 695 matched controls with CRD due to renal calculus and/or cancer, but with normal renal functions. Sera of both groups were tested for anti-Hantavirus IgG using ELISA with a cell-lysate antigen from Hantanvirus prototype strain 76-118. Only 5/350 of CRF history (1.4%), & 7/695 controls (1.0%) were

positive with a titer > or =1:400, but without significant (P= 0.48). All antibody-positive cases and controls were exposed to rodents. They concluded that Hantavirus seroprevalence in CRD patients was low, and didn't appear to be a significant cause of CRF.

Egyptian mammals were reported by many authors. Alpini (1735) wrote the first book on Egyptian mammals. Wassif *et al.* (1944-72) wrote a series of paper on bats, rodents, and local faunal lists. Osborn and Helmy (1980) reported and illustrated land mammals in Egypt and Sinai Peninsula, distributed in nearly all old world. Morsy *et al.* (1988) revised and gave keys for the rodents in Sinai Peninsula, reported allover Egypt and the regional countries

Bat dates to earliest times in ancient Egypt and have its origins in Late Paleolithic cattle herding cultures. Bat was chief goddess of Seshesh, otherwise known as Hu or Diopolis Parva, the 7th Nome of Upper Egypt. Bats (Chiroptera) comprised about 1,200 species worldwide, accounted to one-fourth of all mammal species, and their global distribution, abundance, fly and migrate over large distances, and sociality favor acquisition and spread of many zoonotic infectious diseases mainly viruses (Turmelle and Olival, 2009). Dietz (2005) gave an illustrated key for the Egyptian bats (22 species of eight families). Many authors dealt with bats as reservoirs of zoonotic infectious diseases *Nycteria medusiformis, Trypanosoma vespertilionis,* ectoparasites and *Leishmania* antibodies (Morsy *et al*, 1986a, b, c; 1988, respectively), other zoonotic diseases were reported (Saoud and Ramadan, 2009: Miragli, 2019; El Taweel *et al,* 2020). Also, migratory birds including brown necked raven (Mazyad *et al,* 1999) annually introduce many arthropod-vectors and zoonotic diseases to Egypt (Khalil *et al,* 2011).

Recommendations

1- Among HCPS agents, risky forms are associated with Sin Nombre virus (SNV) and Andes virus. Case-fatality ratios of HCPS were 30-50% for severe forms and 10-30% for milder ones. Hantaviruses pass in urine, feces, or saliva of acutely-infected rodents. It is suspected that much, if not all, transmission to man occurs via the aerosol route.

2- Typically a period of three weeks elapses between exposure to a Hantavirus and first symptoms. Syndrome is characterized by a nonspecific prodrome, followed by abrupt development of non-cardiogenic pulmonary edema and hemodynamic compromise. Cardiorespiratory phase of HCPS can emerge almost as quickly and dramatically as onset, in as little as 24 to 48 hours.

3- Laboratory abnormalities: thrombocytopenia, leukocytosis, hemoconcentration, hypoalbuminemia, and increase in LDH sera. Simultaneous appearance of thrombocytopenia, a left-shifted granulocytic series, and an immunoblast count exceeds 10% of total lymphoid series is referred to diagnostic triad.

4- HCPS must be suspected in settings were in a patient from a rural area or with potential exposure to wild rodents presents with fever, chills, and myalgias. Specific serologic diagnosis should be in patients with bilateral interstitial infiltrates, thrombocytepenia, leukocytosis with a left-shifted granulocytic series, or elevated LDH.

5- Treatment for HCPS is mainly supportive. This includes intensive care unit monitoring and the initiation of mechanical ventilation as needed to treat respiratory failure secondary to capillary leak.

6- Early use of vasopressors for management of hypotension and cautious use of intravenous fluids due to the associated capillary leak syndrome (Grade 1C).

7- No specific antiviral therapy for hantavirus is available. An NIH sponsored randomized, placebo-controlled ribavirin trial was terminated early due to slow accrual. They concluded, that although the study lacked adequate power to determine whether ribavirin was safe or effective, the lack of trends favoring its use suggested that ribavirin did not have a significant role in treatment of Hantavirus cardiopulmonary syndrome.

8- Based upon these observations, the use of

ribavirin off protocol cannot be recommended for established HCPS (Grade 1C).

9- Extracorporeal membrane oxygenation (ECMO) is utilized in centers with expertise in HCPS based upon uncontrolled, but promising clinical experience.

10- ECMO be considered in patients with a cardiac index <2.5 L/min/m^2 despite use of inotropic agents, in specialized centers with available techniques (Grade 2C).

11- Given limited treatment options and high mortality rates, emphasis needs to on avoidance of exposure to potentially infectious rodents, particularly in indoor spaces.

So what about Egypt and regional countries?

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