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Hepatitis C – the need for changes in the system in the health care in Poland

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Ebola viral hemorrhagic fever

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ABSTRACT

Pathogens causing transmissible viral hemorrhagic fevers are therefore classified internationally at the most dangerous hazard level. Most of them may be transmitted through the respiratory tract into human being. For this reason aerosol dissemination of viral pathogens may be considered as biological weapon. The clinical presentation of Ebola virus-infected patients is difficult to distinguish from other infections in the first steps of disease. A rash develops in 25–52% of patients in the first week and hemorrhagic manifestations are noted in some patients after a few days of illness. Tetherin/BST-2 has been identified as an effective cellular factor that prevents Ebola virus hemorrhagic fever as similarly the newly introduced Zmapp. Two proposals vaccines - cAd3-EboV (cAd3) produced by GlaxoSmithKline, and the US National Institute of Allergy and Infectious Diseases and rVSVΔG-EboV-GP (rVSV) produced by NewLink Genetics and Public Health Agency of Canada – were discussed in the last period as effective in prevention of Ebola virus hemorrhagic fever.

Viral hemorrhagic fevers (VHFs) are a diverse group of illnesses characterized by fever and bleeding diathesis. VHFs are severe viral infections, which can cause haemorrhage, multi-organ failure and high case-fatality rates in humans.

Diseases are caused by lipid-enveloped single-standed RNA viruses from four viral families: Arenaviridae, Bunyaviridae, Flaviviridae, and Filoviridae[1]. They are unified by their potential to present as a severe febrile disease with hemorrhagic symptoms and accompanied by shock, and are capable of causing long-lasting and slow burning epidemics, which can interrupt the normal life, commerce or social structure of a community[2].

These viruses are spread in variety of ways – through blood or body fluid exposure. More of them are transmitted from animals to human by a vector, inhalation or ingestion of excretions or secretions. Most of them may be transmitted through the respiratory tract into human being. For this reason aerosol dissemination of viral pathogens may be considered as biological weapon[1].

Some of viruses are directly transmissible from human to human, and can cause outbreaks, or wider transmission, in non-endemic countries. Pathogens causing transmissible VHFs are therefore classified internationally at the most dangerous hazard level, requiring the highest level of laboratory containment (BSL-4 - biosafety level 4). They are grouped together with other dangerous pathogens, some of which may be deliberately released in acts of bioterrorism[3].

FILOVIRIDAE – EBOLA (EBOV) AND MARBURG (MARV) VIRUSES

Filovirus infection results in a spectrum of illness, but most recognized infections present as severe acute febrile illness with bleeding into internal cavities and organs. These viruses are unique among human pathogens. They are filamentous, single-stranded, negative-sense RNA viruses. EBOV is genetically and phenotypically similar to MARV, but the viruses are distinct, with little or no natural crossimmunogenicity between them[2].

EBOV is a member of the family Filoviridae in the order Mononegavirales (MNV), and causes a lethal hemorrhagic fever in both humans and non-human primates. Five species of EBOV have been defined to date on the basis of genetic divergence: Zaireebolavirus (ZEBOV), Sudanebolavirus (SEBOV), TaiForestebolavirus (TFEBOV), Restonebolavirus (REBOV), and Bundibugyoebolavirus (BEBOV). ZEBOV, SEBOV, TFEBOV, and BEBOV cause clinical symptoms in humans and non-human primates, while REBOV causes disease only in non-human primates, and not in humans[4].

Electron microscopic studies have indicated that EBOV is morphologically pleomorphic. The genome is approximately 19 kb in length and encodes the viral proteins in the order NP–VP35–VP40–GP/sGP–VP30– VP24–L. The VP40 and VP24 proteins are viral matrix proteins and are associated with the virion envelope [5]. VP40 is the most abundant protein in the virion and plays a key role in virus assembly and budding as viral matrix protein[6].

Hypothesis of Ebola virus transmission at the human-animal interface is based upon observations in outbreaks countries. The virus maintains itself in fruit bats, which spread the virus during migration. Next, infected fruit bats enter in direct or indirect contact with other animals (gorillas, chimpanzees and other monkeys or mammals e.g. forest antelopes) and pass on the infection. Humans are infected either through direct contact with infected bats (rare event) or through contact with infected dead or sick animals found in the forest (more frequent). Secondary human-to-human transmission occurs through direct contact with the blood, secretion, organs or other body fluids of infected persons, especially after handling dead bodies (funerals)[3].

CLINICAL PICTURE

The typical clinical presentation consists of acute onset of a non-specific febrile illness, including chills, headache, myalgia, nausea/vomiting, and diarrhea. A rash develops in 25–52% of patients in the first week and minor hemorrhagic manifestations are noted in some patients after a few days of illness (petechiae, ecchymoses, bleeding from puncture sites). In many instances, a biphasic pattern can occur, with a brief remission followed by a recurrence of fever and more severe late stage disease. In later stages of the severe forms of illness, patients demonstrate hypotension, shock, mucosal hemorrhages (typically from the gastrointestinal tract) and multi-organ system (particularly renal) failure[1]. Autopsies demonstrate multifocal necrosis. Severe cases are frequently fatal, with ultimate demise attributed to the systemic effects of a septic shock-like syndrome. No licensed or approved specific medical countermeasures exist, making supportive care the cornerstone of patient management[3].

MANAGEMENT AND TREATMENT

The clinical presentation of filovirus-infected patients is difficult to distinguish from other infections, especially early in the clinical course.

Antibiotics were used to prevent and treat secondary bacterial infections. Acyclovir was used in one patient in the 1976 Zaire outbreak, and ribavirin was given to one patient in Russia. No other employments of antiviral drugs were documented. Analgesics, antipyretics, and antiemetic drugs were typically available and administered as needed. Unfortunately, many patients did not receive any further care. Other symptomatic treatments occasionally available included antidiarrheal drugs, sedatives, and antipsychotic drugs to reduce anxiety and agitation. Oral rehydration was typically preferred to administration of intravenous fluids, partially due to the perceived risk of transmission associated with the use of needles as well as resource constraints. Fluid and electrolyte monitoring and supplementation were universally applied to patients, but these measures were not routinely available during most outbreaks[7].

ANTIBIOTICS

Tetherin/BST-2 (also known as CD317 or HM1.24) has been identified as an effective cellular factor that prevents human immunodeficiency virus (HIV)[8]. Tetherin/BST-2 also efficiently inhibits the egress of virus-like particles (VLPs) of Marburg virus and Lassa virus and retains VLPs on the cell surface. The sequestration of tetherin/BST-2 in the specific intracellular compartment may be one of the mechanisms of antagonism by Ebola GP. So far, the mechanism by which EBOV glucoprotein (GP) antagonizes tetherin/BST-2 remains unclear. Further investigations are required to understand the mechanism by which EBOV GP counteracts the antiviral function of tetherin/BST-2. It has been reported that high-level expression of tetherin/BST-2 inhibits ZEBOV production even in the presence of GP [9]. Tetherin/BST-2 has great potential for the development of novel antiviral therapeutic strategies against EBOV infection.

The newly introduced ZMapp preparation by Mapp Biopharmaceuticals Inc. is composed of three groups of monoclonal antibodies directed against Ebola virus, but only in relation to the Zaire subtype. It has not yet been fully approved by the FDA (Food and Drug Administration) and the EMA (European Medicine Agency), but it creates a real hope for patients[10,11].

VACCINES

No specific treatment or vaccine is yet available for Ebola hemorrhagic fever. Several potential vaccines are being tested but it could be several years before any is available. A new drug therapy has shown some promise in laboratory studies and is currently being evaluated. Recently at a meeting in Geneva of 70 scientists, public health and the pharmaceutical industry discussed two proposals vaccines - cAd3-EboV (cAd3) product manufactured by GlaxoSmithKline, and the US National Institute of Allergy and Infectious Diseases (NIAID) and rVSVΔG-EboV-GP (rVSV) product NewLink Genetics and Public Health Agency of Canada. Both vaccines showed 100% efficacy in animal studies[12].

SUPPORTIVE THERAPY

Various blood products, clotting factors, inhibitors of fibrinolysis (ε-aminocaproic acid) and regulators of coagulation were administered to counteract hemorrhage. Transfusion of blood components included whole blood, packed red blood cells, fresh frozen plasma, and platelets. Clotting factors and other regulators of coagulation administered included fibrinogen, and prothrombin, proconvertin, Stuart-factor and antihemophilic globulin B, and vitamin K. In contrast, anticoagulants (heparin) and rheologic agents (pentoxyfylline) were given in some patients to prevent thrombosis and disseminated intravascular coagulation[1,13].

Support for organ failure, including dialysis, hemofiltration, intubation, and mechanical ventilation was only available for a small number of patients in developed-country settings. ■

ANTIBIOTICS WERE USED TO PREVENT AND TREAT SECONDARY BACTERIAL INFECTIONS. ACYCLOVIR WAS USED IN ONE PATIENT IN THE 1976 ZAIRE OUTBREAK, AND RIBAVIRIN WAS GIVEN TO ONE PATIENT IN RUSSIA.

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