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Current Status and Challenges for the Treatment of Japanese Encephalitis

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Abstract—*Japanese encephalitis (JE) is the key cause of viral encephalitis around the globe of Asia. The JE virus is a flavivirus related to yellow fever and Western Nile viruses. The virus exists in a cycle between mosquitoes, domestic swines water birds. Human beings get infected when shown aggression towards an infected insect. The illness is predominantly found in rural and peri urban configurations. Most JE virus attacks are mild (fever and headache) or without obvious symptoms, but approximately one particular in 200 infections results in severe disease indicated by rapid start high fever, headache, neck disorientation, coma, seizures, spastic paralysis and death. The case fatality rate is often as high as 30% among those with disease symptoms; 20-30% of those who survive suffer long lasting neuropsychiatric sequelae. In areas where the JE virus is common, encephalitis occurs mainly in young children because older kids and adults have already been infected and are immune. No effective antiviral therapy exists to treat this flavivirus infection. The production of the only vaccine that was internationally licensed, JE-VAX, was ceased in 2005. Therefore a shortage of Japanese encephalitis vaccines might occur. There are 4 main types of JE vaccines currently in use. This paper describes the current scenario, available treatments and challenges for the treatment of Japanese encephalitis.*

1. INTRODUCTION

JE is caused by neurotropic Japanese Encephalitis Virus (JEV) which belongs to flaviviridae family and is the most important encephalitis causing virus in Asia. It is transmitted by mosquitoes in humans causing inflammation of the membranes around the brain. Japanese encephalitis is a leading cause of viral encephalitis in Asia generally spread from western pacific region in east to Pakistan in west and from Korea in north to Papua New Guinea in south. JEV is reported to cause 35-50 thousand cases and 10-15 thousand deaths annually. Viruses belonging to the flaviviridae primarily spread through arthropod vectors, and is the major cause of one of the most fatal disease around the globe. Flaviviruses are small RNA viruses transmitted by mosquitoes and ticks. Upon entering the host, they take over host cell machinery in order to propagate and flourish. JEV generally affects small children (<15 yrs) and elderly people (>65 yrs) who have weak immune system and hence are vulnerable. JEV infection was initially reported in Southeast Asia but now it is affecting populations worldwide .JEV leads to major outbreaks in tropical regions of Asia with China, Japan, Korea, Philippines, Southeastern Asia and India. JE's mortality rate is almost 25-30%. Some effects such as learning difficulties and behavioral problems can remain masked for several years. From total JE infected patients, nearly one-third die and half of the survivors are left with irreversible neurological damages. Around three billion people are residing in risk prone areas without any vaccination and the number of unvaccinated individuals is continuously increasing. Viruses have evolved various mechanisms to disrupt the host immune system. One important amongst them is preventing the infected cells from sending out chemotactic signals to activate the adaptive immune response.

Japanese encephalitis Virus classification

Group: Group IV ((+)ssRNA)

Family: Flaviviridae

Genus: Flavivirus

Species: Japanese encephalitis virus

It is an infection of the brain caused by the mosquito-borne Japanese encephalitis virus (JEV).JEV is a virus from the family Flaviviridae, part of the Japanese encephalitis serocomplex of 9 genetically and antigenically related viruses, some which are particularly severe in horses, and four known to infect humans including West Nile virus.

The positive sense single-stranded RNA genome is packaged in the capsid which is formed by the capsid protein. The outer envelope is formed by envelope protein and is the protective antigen. It aids in entry of the virus into the inside of the cell. The genome also encodes several nonstructural proteins (NS1, NS2a, NS2b, NS3, N4a, NS4b, NS5). NS1 is produced as secretory form also. NS3 is a putative helicase, and NS5 is the viral polymerase. Japanese encephalitis infects

the lumen of the endoplasmic reticulum (ER)and rapidly accumulates substantial amounts of viral proteins for the Japanese Encephalitis.

Its a zoonotic illness with man as a dead end. The natural host is the pig and the reservoirs of virus are migratory birds of Ardridae family (Cattle egrets, Pond Herons). The virus which is 45-50 nm RNA virus having 3 structural proteins and five non-structural proteins, is transmitted from birds to pigs by mosquitoes of cutex family (Culex vishnui and culex tritaeniohyclinus). It is a rural mosquito which breeds in stagnant water in rice fields. Man is an accidental host in the transmission cycle. When viral load in mosquito gets heavy, man gets infected by its bite. But man to man transmission does not occur.

2. EPIDEMIOLOGY

Japanese encephalitis (JE) is the leading cause of viral encephalitis in Asia, with up to 70,000 cases reported annually.Case-fatality rates range from 0.3% to 60% and depend on the population and age. Residents of rural areas in endemic locations are at highest risk; Japanese encephalitis does not usually occur in urban areas.

Two epidemiological patterns of JE are recognized: epidemic and endemic Epidemic patterns observed mainly in northern areas (Bangladesh, Bhutan, People's Republic of China, Taiwan, Japan, South Korea, North Korea, Nepal, northern Vietnam, northern India, northern Thailand, Pakistan, and Russia) demonstrate typical seasonal characteristics with occasional outbreaks.

Endemic patterns found in southern areas (Australia, Burma, Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Papua New Guinea, Philippines, Singapore, southern Vietnam, southern Thailand, southern India, Sri Lanka, and Timor-Leste) occur sporadically throughout the year.

24 countries in the WHO South-East Asia and Western Pacific regions have endemic JEV transmission, exposing more than 3 billion people to risks of infection with approximately 13 600 to 20 400 deaths. JE primarily affects children. Most adults in endemic countries have natural immunity after childhood infection, but individuals of any age may be affected.

Countries which have had major epidemics in the past, but which have controlled the disease primarily by vaccination, include China, South Korea, Japan, Taiwan and Thailand. Other countries that still have periodic epidemics include Vietnam, Cambodia, Myanmar, India, Nepal, and Malaysia. In the United States, Japanese encephalitis mostly develops among travelers returning from endemic countries.

In India first epidemic was noted in 1955 in Tamil Nadu and it is now endemic in Karnataka,

Andhra Pradesh, West Bengal, Pondicherry, Goa, Maharashtra, UP, Bihar and North Eastern States. There had been 116 deaths reported in Odisha's backward Malkangiri district of India in 2016.A vaccination drive against JE was launched on 5 december in Malkangiri district. JE has claimed the lives of thousands of children in Western Uttar Pradesh – in and around Gorakhpur.

3. SYMPTOMS

The Japanese encephalitis virus (JEV) has an incubation period of 2 to 15 days and the vast majority of infections are asymptomatic: only 1 in 250 infections develop into encephalitis .Fever, headache and malaise are other non-specific symptoms of this disease which may last for a period of between 1 and 6 days. Signs which develop during the acute encephalitic stage include neck rigidity, cachexia, hemiparesis, convulsions and a raised body temperature between 38–41 °C (100.4–105.8 °F). Mental retardation is usually developed.

Mortality of this disease varies but is generally much higher in children. Transplacental spread has been noted. Lifelong neurological defects such as deafness, emotional lability and hemiparesis may occur in those who have had central nervous system involvement. In known cases, some effects also include nausea, headache, fever, vomiting and sometimes swelling of the testicles.The onset of this disease is marked by severe rigors.

More severe infection symptoms: rapid onset,headache, high fever, neck stiffness, stupor, disorientation, coma, tremors occasional convulsions (especially in infants): spastic paralysis, flaccid paralysis - rarely, asymptomatic, nausea, vomiting, behavioral changes, neurological deficits, increased protein level in cerebrospinal fluid

4. DIAGNOSIS

JE virus IgM antibodies are usually detectable 3 to 8 days after onset of illness and persist for 30 to 90 days, but longer persistence has been documented. Therefore, positive IgM antibodies occasionally may reflect a past infection or vaccination. Serum collected within 10 days of illness onset may not have detectable IgM, and the test should be repeated on a convalescent sample. For patients with JE virus IgM antibodies, confirmatory neutralizing antibody testing should be performed. In fatal cases, nucleic acid amplification, and virus culture of autopsy tissues can be useful. Viral antigen can be shown in tissues by indirect fluorescent antibody staining.[3]

Aetiological diagnosis of Japanese Encephalitis is established by testing

1. Acute phase serum collected early in the illness for the virus specific IgM antibodies (IgM captured Elisa) in CSF or in blood within 4–7 days.

2. Demonstrating the four fold rise IgG. Antibody titres by paired, acute and convalescent sera.

3. If facilities are available, the virus can be identified by PCR (Polymerase chain reaction).

Investigations are required to exclude pyogenic meningitis, Tuberculous meningitis, Cerebral Malaria, Hypoglycemia, dyselectrolytemia, Reye's syndrome and other metabolic condition.

Cerebro Spinal Fluid (CSF) changes in Japanese EncephalitisRoutine investigations like CBP, ESR & CSF do not help much except to exclude pyogenic, Confirmation of the diagnosis is made by demonstrating rising titers of JE specific 1gM antibodies in the CSF by 1gM capture ELISA. A four fold rise in antibody titres is diagnostic. Viral culture generally is not successful.

5. TREATMENT

Treatment aims at relieving the symptoms like pain and reducing the intracranial pressure. No specific treatments have been found to benefit patients with JE, but hospitalization for supportive care and close observation is generally required. Treatment is symptomatic. Rest, fluids, and use of pain relievers and medication to reduce fever may relieve some symptoms.

No specific antiviral drugs for treating Japanese encephalitis are available. It is mainly supportive and includes:

1. Maintenance of vital functions

2. Nutritional support

3 Monitoring of fluid and electrolyte balance

4. Control of seizures (use of phenytoin and barbiturates)

5. Reduction of cerebral edema by use of mannitol, frusemide and cortico steroids.

6. Management of Hyperthermia by use of paracetamol / lytic cocktail.

There are currently no known effective anti-viral agents available to treat JE. Osmotic diuretic, mannitol, suramin, osmitrol, resectisol, JE vaccine, ixiaro, JE-VAX are being used. Apart from this fluid management, control of raised intracranial pressure, anticonvulsants, head elevation, invasive monitoring, controlled ventilation and supportive care are required.

Acyclovir, pleconaril, amantadine, rimantidine, oseltamivir,foscarnet,vidarabine are among the latest treatment for JE. Curcumin has been shown to impart neuroprotection against Japanese Encephalitis infection in an in vitro study.

The use of rosmarinic acid, arctigenin and oligosaccharides with degree of polymerization 6 from Gracilaria sp. or Monostroma nitidum have been shown to be effective in a mouse model of Japanese encephalitis.

Curcumin has been shown to impart neuroprotection against Japanese Encephalitis infection in an in vitro study. Curcumin possibly acts by decreasing cellular reactive oxygen species level, restoration of cellular membrane integrity, decreasing pro-apoptotic signaling molecules, and modulating cellular levels of stress-related proteins. It has also been shown that the production of infective viral particles from previously infected neuroblastoma cells are reduced, which is achieved by the inhibition of ubiquitin-proteasome system.

Minocycline in mice resulted in marked decreases in the levels of several markers, viral titer, and the level of proinflammatory mediators and also prevents blood brain barrier damage. Curcumin has been shown to impart neuroprotection against Japanese Encephalitis infection in an in vitro study.

6. VACCINES

The vaccines are more than 90% effective. Doses are given either by injection into a muscle or just under the skin.[1]One or two doses are given depending on the version of the vaccine. Extra doses are not typically needed in areas where the disease is common. In those with HIV/AIDS or those who are pregnant an inactivated vaccine should be used. Immunization of travellers who plan to spend time outdoors in areas which are prone to Japanese encephalitis.

There are 4 main types of JE vaccines currently in use: inactivated mouse brain-derived vaccines, inactivated Vero cell-derived vaccines, live attenuated vaccines, and live recombinant vaccines.

The vaccines are relatively safe. Pain and redness may occur at the site of injection. As of 2015, 15 different vaccines are available: some are based on recombinant DNA techniques, others weakened virus, and others inactivated virus. The Japanese encephalitis vaccines first became available in the 1930s. One of them was an inactivated mouse brain-derived vaccine (the Nakayama and/or Beijing-1strain), made by BIKEN and marketed by Sanofi Pasteur as JE-VAX, until production ceased in 2005. The other was an inactivated vaccine cultivated on primary hamster kidney cells (the Beijing-3 strain). The Beijing-3 strain was the main variant of the vaccine used in the People's Republic of China from 1968 until 2005.[6]

Three second-generation vaccines have entered markets since then: SA14-14-2, IC51 and Chimeri Vax-JE. The live-attenuated SA14-14-2 strain was introduced in China in 1988.The live-attenuated SA14-14-2 strain was introduced in China in 1988. It is much cheaper than alternative vaccines, and is administered to 20 million Chinese children each year. A purified, formalin-inactivated, wholevirus vaccine known as IC51 (marketed in Australia and New Zealand as JESPECT

and elsewhere as IXIARO) was licensed for use in the United States, Australia, and Europe during the spring of 2009.

All of the vaccines are based on G3 virus strains and have been shown to work well against G1 through G4 strains. However, their efficiency against the previously rare but possibly re-emerging G5 strain is not clear.

The Vero cell-derived purified inactivated JE vaccine–JENVAC, which received manufacturing and marketing approvals from the Drug Controller General of India, is the first vaccine to be manufactured in the public-private partnership mode between the Indian Council of Medical Research and Bharat Biotech. The vaccine will provide increased immunogenicity and long-term protection as a result of unique manufacturing technologies. It is stated by the representatives of the NIV that the success rate of the vaccine is more than 90% and it can be given to people aged between 1–50 years.

Another vaccine, a live-attenuated yellow fever-Japanese encephalitis chimeric vaccine known as ChimeriVax-JE (marketed as IMOJEV) was licensed for use in Australia in August 2010[7] and in Thailand in December 2012.

Inactivated Vero cell culture-derived Japanese encephalitis (JE) vaccine (manufactured as IXIARO) is the only JE vaccine licensed and available in the United States. This vaccine was approved in March 2009 for use in people aged 17 years and older and in May 2013 for use in children 2 months through 16 years of age. Other JE vaccines are manufactured and used in other countries but are not licensed for use in the United States.

IXIARO is given as a two-dose series, with the doses spaced 28 days apart. The last dose should be given at least 1 week before travel. For persons aged 17 years and older, a booster dose may be given if a person has received the two-dose primary vaccination series one year or more previously and there is a continued risk for JE virus infection or potential for reexposure.

Although studies are being conducted on the need for a booster dose for children, data are not yet available.Reactions to JE Vaccine Reactions to IXIARO are generally mild and include pain and tenderness, mild headaches, myalgia (muscle aches), and low-grade fevers.

A breakthrough in the field of Japanese encephalitis therapeutics is the identification of macrophage receptor involvement in the disease severity.

7. PREVENTION

1.Use Insect Repellent. When you go outdoors, use an EPA-registered insect repellent such as those containing DEET, IR3535, picaridin or oil of lemon eucalyptus.

2. Wear Proper Clothing to Reduce Mosquito Bites. When weather permits, wear long-sleeves, long pants and socks when outdoors. Mosquitoes may bite through thin clothing. Don't apply repellents containing permethrin directly to skin.

3. Reduce Exposure to Mosquitoes During Peak Biting Hours. The mosquitoes that transmit JE virus feed mainly outside during the cooler hours from dusk to dawn. Travelers to high risk areas should consider minimizing outdoor activities at these times. To reduce the risk of JE, travelers should stay in air-conditioned or well-screened rooms, or use a bed net and aerosol room insecticides.

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