SENDAI VIRUS

SUMMARY

Etiology
- Sendai virus (SeV) is a paramyxovirus in the genus *Respirovirus*.
- There is a single serotype consisting of numerous strains with varying virulence.

Cleaning and Disinfection
- SeV does not survive well outside of a host.
- Generally, paramyxoviruses are susceptible to acids, alcohols, aldehydes, alkalis, halogens, and oxidizing agents, and have limited susceptibility to biguanides, phenolic compounds, and quaternary ammonium compounds.

Epidemiology
- SeV naturally affects mice, rats, and hamsters. Limited disease in pigs has been attributed to SeV; however, pigs are not thought to be a natural host.
- SeV does not affect humans.
- Laboratory mice in the Americas, Europe, Australia, and Asia are affected by SeV. An outbreak in swine occurred in the early 1950s in Japan. Other emerging paramyxoviruses have been identified in swine in recent years in locations including Canada, the United States, and Germany.
- High mortality rates have been observed in one-month-old pigs infected with SeV experimentally. In the Japanese outbreak, high incidence was observed in 15 districts. However, testing performed several years after the initial outbreak (1957–1958) showed seropositivity of only 2%. Further serological testing in the 1960s was negative in Japan.

Transmission
- Transmission in mice is via direct contact or aerosols. An enzootic cycle exists where suckling mice are infected by older, acutely infected mice, once passive immunity wanes. This cycle persists subclinically in breeding colonies of laboratory mice. SeV can also cause latent infection.
- Both vertical and lateral transmission were seen in the 1950s outbreak in swine in Japan.

Infection in Swine/Pathogenesis
- SeV causes flu-like signs in pigs. Severity of disease is age dependent.
- Infected females can produce stillborn pigs.
- In the 1950s outbreak in Japan, encephalitis was observed in 2 to 4 month-old pigs.

Diagnosis
- Virus isolation is possible with identification via trypsin overlays, immunofluorescence, or hemadsorption.
- Primers and probes have been described for quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR), and numerous commercial SeV PCR kits are available for use in rodents.
- There are numerous commercial enzyme linked immunosorbent assay (ELISA) kits for various laboratory rodent species, but none available for swine.

Immunity
- Lifelong immunity is observed in mice following SeV infection.
- There are no commercial SeV vaccines available for any species, including swine.
- Cross-protection is observed between SeV and human parainfluenza virus type 1.
- Porcine parainfluenza 1 is an emerging virus found in Hong Kong that is closely related to SeV and human parainfluenza virus type 1.

Prevention and Control
- SeV can be transmitted rapidly throughout a rodent colony. Affected colonies are usually culled to eliminate the virus.

Gaps in Preparedness
- There are no commercially available vaccines for SeV.
- Because SeV is an established pathogen of rodents, available diagnostic tests may be adaptable for use in swine.
- Emerging paramyxoviruses in swine must be definitively diagnosed.

OVERVIEW

Sendai virus (SeV) is a paramyxovirus in the genus *Respirovirus*. Other names for SeV are murine parainfluenza virus type 1 and hemagglutinating virus of Japan. SeV is commonly used in biomedical research as a gene vector.

SeV is mainly known as a respiratory pathogen of laboratory rodents (mice and rats); it has a worldwide distribution in laboratories in the Americas, Europe, Asia, and Australia. One large swine outbreak occurred in the 1950s in Japan, with nearly half of all pigs testing seropositive at a central Tokyo slaughter house. However, there were no reported positive cases after 1961 and SeV was not considered a problem in Japan by 1970. In the United States, SeV has been suspected in pigs; however, diagnostic testing identified bovine parainfluenza virus type 3 instead. Another emerging parainfluenza virus, porcine parainfluenza virus type 1, has recently been found in Hong Kong slaughterhouses.

In laboratory rodents, SeV can persist in an enzootic cycle. Suckling mice, protected by maternal antibodies, are not susceptible to infection until after weaning. Older, weaned rodents transmit the virus to younger rodents via direct contact or aerosols. There is limited information available regarding disease in swine. However, SeV is known to cause latent infection of the olfactory neurons in rodents, which facilitates subclinical enzootic cycles. Epizootic infection, with an acute explosion of symptoms throughout a swine herd, can occur in naïve populations.

Like other parainfluenza viruses, SeV infects the respiratory epithelium of affected individuals. Pigs infected with SeV showed flu-like symptoms including fever, coughing, nasal discharge, and anorexia. Fatality rates are highest in pigs less than one-month-old, with two-month-old pigs being much less susceptible to disease. One-month-old pigs can also exhibit stunted growth when affected by SeV. The 1950s outbreak in Japan produced encephalitis-like disease in pigs 2–4 months old.

Virus isolation using trypsin overlays, immunofluorescence, or hemadsorption can be used to definitively diagnosis SeV infection. Inoculation of embryonated chicken eggs can produce recoverable virus. Histopathology is not very sensitive or specific for diagnosis. Primers and probes have been described for quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR), and numerous commercial SeV PCR kits are available for use in rodents.

There are numerous commercial enzyme linked immunosorbent assay (ELISA) kits for various laboratory rodent species, but none available for swine. Different antigenic peptides of the SeV nucleocapsid protein have been described for possible ELISA use, offering high specificity. Indirect immunofluorescence can also be used for antibody detection, and a virus neutralization assay using green fluorescent protein for antibody quantification at a high throughput level has been described. Hemagglutination inhibition and complement fixation assays are not the most sensitive and specific assays, making them a poor choice compared to other available antibody detection methods. Nasopharyngeal secretions have been used to detect parainfluenza virus type 1 from humans, and blood samples should be taken for serological diagnostic tests.

There are no commercial SeV vaccines available for any species. Xenotropic parainfluenza vaccines, using live viruses, have been shown to experimentally protect aberrant hosts from infection. Inoculation with human parainfluenza virus type 1 can protect mice from SeV challenge, and SeV inoculation can protect African green monkeys from live challenge with human parainfluenza virus type 1.

LITERATURE REVIEW

1. Etiology

1.1 Key Characteristics

Sendai virus (SeV) is a paramyxovirus in the genus *Respirovirus*, which normally causes respiratory diseases in laboratory rodents, particularly mice and rats.[1] SeV is also used in biomedical research as a gene delivery vector, pluripotent stem cell inducer, and inducer of cell fusion.[2-4] Other names for SeV include murine parainfluenza virus type 1 and hemagglutinating virus of Japan.[5]

1.2 Strain Variability

There is a single serotype consisting of antigenically homologous SeV strains.[1] There are numerous SeV strains that have been isolated.[1] In mice, strains have been found to have varying degrees of virulence, with some being 1000-fold more virulent than others when comparing median lethal dose.[1]

2. Cleaning and Disinfection

2.1 Survival

SeV is labile and does not survive well outside of a host.[1]

2.2 Disinfection

Paramyxoviruses are susceptible to acids, alcohols, aldehydes, alkalis, halogens, and oxidizing agents, and have limited susceptibility to biguanides, phenolic compounds, and quaternary ammonium compounds.[6]

3. Epidemiology

3.1 Species Affected

SeV can naturally infect laboratory mice, rats, and hamsters.[1] Experimental inoculation can lead to infection in guinea pigs.[1] Outbreaks in pigs occurred in Japan in 1953, but the virus nearly completely disappeared by 1961, suggesting that swine are not a natural host for SeV.[7]

3.2 Zoonotic Potential

In the 1950s, SeV was believed to affect humans, but now those reports have been attributed to human parainfluenza virus type 1 (hPIV1).[1] SeV is not thought to cause disease in humans; however, neutralizing antibodies for SeV can be found in people due to prior infection with hPIV1.[8]

3.3 Geographic Distribution

SeV is distributed worldwide in developed regions in laboratory mice, including the Americas, Europe, Australia, and Asia.[1]

The Japanese SeV outbreak in swine began in January, 1953; subsequent outbreaks occurred at the National Institute of Animal Health in June and July of that year.[5] In early 1955, serum samples tested at a Tokyo slaughterhouse showed 44% SeV prevalence in the country, with 15 different districts having high incidence, indicating nationwide dissemination of SeV.[5] However, when using complement fixation testing from 1957–1958, seropositivity was only 2%.[5] In 1961, about 5% of sera at the Tokyo slaughterhouse was found to be positive.[5] From 1961–1966, serological testing was completely negative in Japan, and SeV was thought to be irrelevant by the Japanese swine industry by 1970.[5]

Since 1970, cases of emerging paramyxoviruses have been found in swine in Canada, the United States, Israel, and Germany.[9] However, isolates from the United States thought to possibly be SeV have been found to be cross-species infection of pigs with bovine parainfluenza virus type 3 strains.[10]

3.4 Morbidity and Mortality

Experimentally infected pigs (unknown age) inoculated with infectious autopsy materials from diseased pigs presented with self-limiting influenza-like symptoms.[5] One-month-old piglets infected with SeV showed high mortality rates, while two-month-old piglets were less affected.[5]

4. Transmission

In mice, SeV can be spread by direct contact and airborne transmission.[12] In mice, an enzootic infection cycle exists where actively immune adults pass on maternal antibodies to suckling mice.[1] The SeV-susceptible suckling mice are protected by maternal antibodies, and can become infected by slightly older, acutely infected mice once their passive immunity begins to wane.[1] This enzootic cycle can persist mostly subclinically in breeding colonies of laboratory mice.[1]

One source of an enzootic outbreak is latent reemergence. In mice, SeV can infect olfactory neurons and persist latently.[13] Latent infections have been found to last for at least 168 days post-infection in experimentally infected mice.[13] SeV directly infects olfactory neurons from the nasal cavity, evidenced by lack of antigen in any other part of the brain outside of the olfactory bulb, and lack of viremia.[13]

An epizootic infection can cause more widespread, acute, clinical illness in a naïve colony of mice.[1] Clinical manifestations and severity of the enzootic cycle of the disease rely on host and environmental factors.[1]

Vertical transmission was seen in Japan with infected pregnant females producing stillborn piglets.[5] In 1953 in Japan, SeV spread throughout swine facilities through introduction of clinically sick pigs, suggesting lateral transmission.[5]

5. Infection in Swine/Pathogenesis

SeV primarily invades the respiratory epithelium of infected animals.[7] It suppresses the pulmonary immune system, leaving infected animals open to secondary bacterial and viral infections.[7] When 2-day-old pigs were experimentally infected with SeV, they died two to four days post-inoculation.[11]

5.1 Clinical Signs

Pigs infected with SeV show flu-like symptoms including transient fever, cough, nasal discharge, and anorexia.[5] Severity of disease is age dependent.[5] Pregnant females produced stillborn piglets when infected.[5]

Encephalitis with muscle trembling, convulsions, and rolling was seen in 2 to 4 month old pigs in December 1953 in Japan.[5] A virus antigenically similar to SeV was recovered after this infection, leading researchers to believe SeV was responsible.[5]

5.2 Postmortem Lesions

Upon necropsy, lung consolidation, patchy hemorrhage, and swelling of the pulmonary hilar lymph nodes were found.[5]

In experimentally infected two-day-old piglets, SeV caused a desquamative pneumonia with peribronchial necrosis.[11] Microscopic lesions show an epithelial cell containing exudate in the alveoli and bronchioles.[11]

The epithelium of the bronchioles can become detached in some regions and become focally proliferative in othes.[11] Peribronchial, necrotic foci can also be observed.[11]

6. Diagnosis

6.1 Clinical History
SeV can be suspected when flu-like signs or encephalitis in young pigs and/or reproductive failures in females are observed.

6.2 Tests to Detect Nucleic Acids, Virus, or Antigens
Virus isolation can be used to definitely diagnose SeV infection.[1] Clinically affected, preferably seronegative individuals should be tested, using sterile lung suspensions or nasal washes.[1] SeV can be detected in various cell lines using trypsin overlays, immunofluorescence, or hemadsorption.[1] SeV inoculated into the amniotic or allantoic sac of 8 to 10 day-old embryonated chicken eggs can produce recoverable virus.[1]

Histopathology is not very sensitive or specific, making it a poor choice for diagnosis.[1] Primers and probes for quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) have been described.[14] There are numerous commercial SeV PCR kits available. Virus titers are highest 4–5 days post infection in mice, and wane to undetectable levels by 10–11 days post-infection.[7]

6.3 Tests to Detect Antibody
IgM antibodies peak at day seven, while IgA and IgG peak titers occur around day 10.[7] Commercial enzyme-linked immunosorbent assay (ELISA) kits are available for detection of SeV for various laboratory rodents, but not have been developed for pigs. Antigenic peptides of the SeV nucleocapsid protein have been described for possible use as a linear antigen in an ELISA to allow SeV diagnosis with higher specificity than whole antigenic virions.[15,16] ELISA can begin to detect antibodies at seven days post-infection.[7] Indirect immunofluorescence can also be used to detect antibodies.[7] A virus neutralization assay has been developed using a green fluorescent protein reporter as a means of antibody quantification at a high throughput level.[8] Hemagglutination inhibition and complement fixation assays are less sensitive and specific, making them a poor choice compared to ELISA or immunofluorescence.[7]

6.4 Samples
6.4.1 Preferred Samples
Nasopharyngeal secretions have been used for viral antigen detection of parainfluenza virus type 1 in people.[17] Blood samples should be taken for serological diagnostic tests.

6.4.2 Oral fluids
There is no data available on the suitability of oral fluids as samples for SeV testing.

7. Immunity

7.1 Post-exposure
Maternal antibodies can protect suckling mice from SeV infection, leaving the mice susceptible to infection after they are weaned and maternal antibody titers have waned.[7] After surviving infection, mice have lifelong immunity to subsequent infections with SeV.[18]

7.2 Vaccines
Intranasal immunization with SeV has shown to protect African green monkeys against a challenge with live hPIV-1.[19] Inversely, intranasal immunization with hPIV-1 has shown to protect mice against

challenge with live SeV.[18] There are no licensed vaccines available for SeV in any species.[12] Using xenotropic parainfluenza viruses may potentially be useful in the future for immunization.

7.3 Cross-protection
There is cross-protection between SeV and hPIV-1, as SeV neutralizing antibodies were found in humans across four different continents.[8] A newly emerged paramyxovirus, porcine parainfluenza virus 1 (pPIV1), has been found in approximately 3% of slaughtered swine in Hong Kong.[20] pPIV1 is very closely related with SeV and hPIV1, making it a potential confounding factor in diagnosis of an outbreak of paramyxovirus in swine.[20]

8. Prevention and Control
In mice, SeV can be rapidly spread through direct contact and aerosolization of infectious particles, making containment a challenge. Breeding colonies of laboratory rodents affected by SeV are commonly culled to completely rid the facility of SeV.[7] Pigs with latent SeV could possibly spread the disease to new, naïve pigs brought to a facility.[7]

9. World Organization for Animal Health (OIE) Terrestrial Animal Health Code
SeV is not included in the 2015 OIE Terrestrial Animal Health Code. There are no restrictions on importation of animals from countries or zones infected with SeV.

10. Gaps in Preparedness
No experimental or commercially-licensed vaccines for SeV are available. SeV is an established pathogen of laboratory rodents, making diagnostic tests for rodents available and potentially adaptable for use in swine in an outbreak. Because of the possibility of cross-infection with bovine parainfluenza type 3 (bPIV3) or infection with pPIV1, differentiating between bPI3, pPIV1, and SeV should be part of the initial confirmation of any newly found paramyxovirus infecting swine.

ACKNOWLEDGEMENTS

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