

Infectious Salmon Anemia

Hemorrhagic Kidney Syndrome

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Importance

Infectious salmon anemia (ISA) is one of the most important viral diseases of farmed Atlantic salmon. This highly contagious disease can be insidious, with an initially low mortality rate; however, the cumulative mortality can sometimes exceed 90% if the disease remains unchecked. Infectious salmon anemia was first described in Norway in 1984, and it continues to be a problem in that country despite control measures. Since the late 1990s, outbreaks have also been reported in other locations. This disease devastated the salmon industry of the Faroe Islands in 2000, and an epizootic in Scotland in 1998-1999 cost an estimated \$32 million (U.S.) to eradicate. ISA has been a recurring problem in Chile, the Cobscook Bay in Maine, and the Bay of Fundy in New Brunswick, Canada. In New Brunswick, it results in annual losses of approximately \$4.8–\$5.5 million (U.S) to farmers, and millions of fish have been culled in control efforts. New outbreaks can also occur in areas where this disease was absent for many years. In 2009, an outbreak was reported again in Scotland.

Understanding of the epidemiology of ISA is still incomplete, which complicates its control. The reservoirs for the virus are not known, but experiments have shown that several species of salmonids can carry virulent ISA viruses asymptotically. These viruses might cause outbreaks if they are transmitted to farmed Atlantic salmon. Noncultivable, apparently nonpathogenic, isolates have also been detected in wild salmonids. Small changes in these viruses, analogous to the mutations that allow low pathogenicity avian influenza viruses to become highly pathogenic, may allow them to become more virulent. Some evidence suggests that certain ISA viruses may cause illness in species other than Atlantic salmon. One virus was isolated from sick farmed Pacific Coho salmon in Chile in 1999, and a highly virulent strain can cause disease in experimentally infected rainbow trout.

Etiology

Infectious salmon anemia virus (ISAV) is a member of the genus *Isavirus* in the family Orthomyxoviridae. Hemorrhagic kidney syndrome is an old name for the disease in Atlantic salmon.

The two major lineages of ISAV are the European genotype (or genotype I) and the North American genotype (or genotype II). Various clades occur within these genotypes. A small, highly polymorphic region (HPR) of the viral hemagglutinin-esterase (a surface glycoprotein encoded by genomic segment 6) can be used to classify ISAV isolates into numbered groups. HPR0 and HPR00 consist of the viruses that can be detected in fish by reverse transcription polymerase chain reaction (RT-PCR) assays, but cannot be cultured in the currently used cell lines. These viruses seem to be nonpathogenic for Atlantic salmon and other salmonids. Viruses with deletions in the HPR (e.g., those viruses classified as HPR1, HPR2, HPR3, etc.) appear to be more virulent and can be isolated in cell culture. A number of HPR genotypes have been detected.

Species Affected

Outbreaks of infectious salmon anemia occur in farmed Atlantic salmon (*Salmo salar*). Wild Atlantic salmon might also be susceptible. Rarely, isolates have been reported to affect other salmonids. One virus was linked to an illness among coho salmon (*Oncorhynchus kisutch*) in Chile in 1999, by both virus isolation and serology. ISAV has not been reported from any disease outbreaks in coho salmon since that time. A different ISAV isolate caused clinical signs in experimentally infected rainbow trout (*O. mykiss*). The latter isolate was highly virulent for Atlantic salmon, but it infected coho salmon subclinically.

The reservoir hosts for ISAV are unknown. In experiments, isolates that are virulent for Atlantic salmon usually infect other fish asymptotically. Subclinical infections with these isolates have been reported in salmonids including brown trout (the freshwater resident form of *Salmo trutta*), sea trout (the migratory form of *S. trutta*), rainbow trout (the freshwater resident form of *O. mykiss*), steelhead trout (the migratory form of *O. mykiss*), chum salmon (*O. keta*), Chinook salmon (*O. tshawytscha*), coho salmon (*O. kisutch*) and Arctic char (*Salvelinus alpinus*), as well

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as some non-salmonids such as herring (*Clupea harengus*) Atlantic cod (*Gadus*) and pollock (*Pollachius virens*). Non-cultivable (HPR0 or HPR00) isolates have been detected in asymptomatic wild or feral fish such as brown trout, sea trout, Atlantic salmon and rainbow trout. Salmonids including brown trout and sea trout, which can carry ISAV viruses asymptotically for long periods, and wild Atlantic salmon, have been proposed as possible reservoir hosts.

Geographic Distribution

Infectious salmon anemia outbreaks occur periodically in Norway and Chile, as well as in a limited region of North America shared by the U.S. and Canada. In North America, this disease currently seems to be limited to the Bay of Fundy in New Brunswick, the Cobscook Bay area of Maine, and Passamaquoddy Bay, which is shared by Maine and New Brunswick. Outbreaks have been reported occasionally in other countries, including the Faroe Islands and Scotland. This disease is suspected to occur in Iraq. Noncultivable, apparently nonpathogenic (HPR0 or HPR00), isolates of ISAV have been reported in wild salmonids in several countries, states or provinces including Norway, Scotland, Ireland, New Brunswick, Nova Scotia, Maine and Chile. These noncultivable isolates probably also occur in some areas where fish have not been tested.

The North American and European genotypes are not confined to their respective geographic areas. In Chile, ISA viruses of the European genotype have caused infectious salmon anemia in Atlantic salmon, but the virus isolated from coho salmon in 1999 was of the North American genotype. Most of the ISA viruses that have been detected in Canada and the U.S. belong to the North American lineage, but avirulent (HPR0) viruses from the European lineage have also been found in both countries.

Transmission

Horizontal transmission of ISAV occurs readily within a tank or net pen. Transmission also takes place, although more slowly, between salmon in different nets at a site, as well as between farms. ISAV probably infects fish through the gills, but ingestion has not been ruled out. This virus is shed in epidermal mucus, urine, feces and gonadal fluids. In one study, virus shedding was first detected 7 days after inoculation, and rose above the minimum infective dose on day 11, two days before the first deaths occurred. Shedding peaked approximately 15 days after inoculation, when mortalities were high. ISAV also occurs in blood and tissues; tissue wastes from infected fish are infectious. ISAV replicates best at the cold temperatures where salmon thrive (5-15°C [41-59°F]). The optimal growth temperature for this virus in cell lines is 10-15°C (50-59°); it does not replicate when the temperature is 25°C (77°F) or higher. Fish that survive the illness can shed the virus for more than a month.

Epidemiological studies suggest that ISAV can be transmitted indirectly in water and on fomites, as well as by close contact between fish. Horizontal transmission can occur in both freshwater and seawater. Sea lice (*Lepeophtheirus salmonis* and *Caligus* sp.) may be mechanical vectors. These parasites could also increase the susceptibility of fish by increasing stress. In the laboratory, ISAV remained infective when held at 15°C (59°F) for 10 days or 4°C (39°F) for 14 days. There was a three log (thousand-fold) reduction in the viral titer when ISAV was held at 4°C for 4 months. It was stable between pH 5.7 and pH 9.0. Because the virus's survival can also be affected by factors such as UV irradiation and components in the water which can either bind or inactivate it, it is difficult to estimate the length of time before ISAV is inactivated in nature.

Whether vertical transmission occurs is controversial. There is no definitive evidence for this route, and ISAV was not transmitted in eggs in one experiment. The consensus has been that vertical transmission is unlikely. Nevertheless, a few epidemiological studies, including some recent genetic studies, suggest that fish might be infected early in life. One possibility that has been suggested is that only avirulent strains are transmitted vertically. Transmission in ovarian fluids might also be possible.

The source of the virus in outbreaks is not always known. Atlantic salmon are farmed at sea in net cages; they are not completely isolated from wild species, and can come in close contact with animals small enough to cross the net. Wild fish might act as carriers. Virulent isolates of ISAV can be detected in asymptomatic brown trout, sea trout, rainbow trout and herring for weeks after intraperitoneal injection. (However, replication is limited in herring.) In sea trout, viral RNA could still be found 135 days after infection. Blood from a brown trout, taken 7 months after it had been infected, caused disease when it was injected into Atlantic salmon. ISAV can also be transmitted from salmon to trout, and from trout to salmon, when these species are in the same tank. Arctic char clear this virus more quickly than rainbow trout or brown trout. It has also been found for a short time in non-salmonids. Nucleic acids could be detected in juvenile Atlantic cod for up to 45 days after intraperitoneal injection. Pollock have been suggested as potential carriers, because they are common in and around Atlantic salmon net pens. However, pollock were found to clear the virus within a week of injection, and are unlikely to be reservoirs. It is possible that virulent ISA viruses are generated from avirulent strains that circulate among wild salmonids and other species.

Incubation Period

Clinical signs have been reported in 2 to 4 weeks in some experimentally infected fish.

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Clinical Signs

In farmed Atlantic salmon, the clinical signs may include lethargy, anemia, leukopenia, ascites, exophthalmia, darkened skin and increased mortality. In some cases, the hematocrit may be nearly normal; in others, severe anemia with a hematocrit as low as 2-3% may be seen. As a result of the anemia, the gills may be pale. Hemorrhages may be found in the anterior chamber of the eye. Jaundice on the ventral portion of the body has been reported among Atlantic salmon in Chile.

Similar signs, including anemia and pale gills, were seen in the outbreak among farmed coho salmon in Chile. Jaundice, with yellowing of the base of the fins and on the abdomen, was also reported.

In experimentally infected rainbow trout, the clinical signs included ascites, exophthalmia and hemorrhages at the base of fins. The hematocrit was decreased, but these fish did not become anemic and the gills were not pale. Deaths occurred sporadically among rainbow trout up to 46 days after inoculation. The cumulative mortality rate was lower than in Atlantic salmon, which died rapidly when injected with the same virus.

Post Mortem Lesions

In Atlantic salmon, the gills may be pale and the skin can be darkened. Exophthalmia may also be seen. Yellow- or blood-tinged fluid may be found in the peritoneal and pericardial cavities. Petechiae, which may be extensive, can usually be found on various organs and tissues, including the eye, the internal organs, the visceral fat and the skeletal muscles. The spleen may be enlarged and congested. Congestion, enlargement and necrosis may also be apparent in the liver; in some cases, this organ may become dark brown or black, and it may be covered with a thin layer of fibrin. The kidney may be swollen and dark; blood and liquid may exude from the cut surface. The gastrointestinal tract may also be congested, but blood is not usually found in the intestinal lumen if the carcass is fresh. The histopathological lesions may include hemorrhagic necrosis of the liver, renal interstitial hemorrhages and tubular nephrosis, filamental sinus congestion of the gills, splenic congestion with erythrophagocytosis, and congestion of the lamina propria of the stomach and foregut.

Unusual characteristics noted during the 2007-2008 outbreak among Atlantic salmon in Chile were the absence of profound interstitial hemorrhages in the kidney, and the occurrence of hydropericardium and severe myocarditis. Prominent heart lesions had previously been reported only in experimentally infected rainbow trout, and not in Atlantic salmon. The salmon in Chile were recovering from piscirickettsiosis, and it is not known whether this disease may have contributed to the unusual signs. Other lesions were consistent with ISA outbreaks reported among Atlantic salmon in other countries.

In coho salmon in Chile, the gross lesions were similar to those seen in Atlantic salmon, but jaundice was apparent, and the liver and gall bladder were pale.

In experimentally infected rainbow trout, the lesions included ascites, petechiae in visceral adipose tissues, exophthalmia and hemorrhages at base of the fins. The liver and spleen were congested in a minority of these fish. Unlike Atlantic salmon, relatively few rainbow trout had obvious liver necrosis or kidney necrosis on histopathology, and some trout had epicarditis, endocarditis and myocarditis.

Morbidity and Mortality

Subclinical infections may be common among salmonids in some locations. A recent study in Norway detected ISAV in 22 of 24 Atlantic salmon smolt production sites by real-time RT PCR. In this study, more than one isolate was found in some smolt populations and at one marine site. In Norwegian rivers, the prevalence of apparently nonpathogenic strains in wild salmonids was highly variable; in some cases, the virus was detected in only a single fish, while in others, it was found in 100% of the fish tested. Similarly, the distribution of the virus was not homogeneous among wild fish in Scotland.

Disease usually occurs among salmon in their marine stage; outbreaks have rarely been reported among young fish in freshwater. One freshwater outbreak was attributed to contamination from raw seawater. Although infectious salmon anemia is possible at any time of the year, seasonal effects have been reported by some authors. Mortality is reported to peak in early summer and winter. The disease often begins in one or two net pens, and it may not spread to other pens for months. The onset of the illness may be affected by management factors such as the water temperature, the amount of time the fish have been in saltwater, nutrition, infestation by sea lice and other stressors. Outbreaks can be precipitated or exacerbated by handling fish on infected farms. The genotype of the fish may affect their susceptibility.

The morbidity and mortality rates are highly variable. Few fish may be affected at the beginning of an outbreak; the initial daily mortality is often 0.5 to 1%. If the spread of the virus remains unchecked, mortality can increase either gradually or suddenly. Cumulative mortality varies from insignificant to moderate or severe; highly virulent viruses may kill more than 90% of the fish over a few months. Limited data suggest that the survivors may have some resistance to infection with other isolates. Infectious salmon anemia can be reproduced in experimentally infected wild Atlantic salmon; however, one study has suggested that they are less susceptible than farmed salmon. The difference in susceptibility might be genetic, or it could result from increased stress in farmed populations. Whether clinical signs occur among Atlantic salmon in the wild is unknown.

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Only two isolates of ISAV have been reported to affect salmonids other than Atlantic salmon. One virus was linked to an illness among coho salmon but not Atlantic salmon in Chile in 1999. A different isolate was pathogenic in Atlantic salmon, and to a lesser extent, in experimentally infected rainbow trout. A high dose of this virus killed 80% of the inoculated salmon and 36% of the rainbow trout. At a low dose, the mortality rate was 67% in Atlantic salmon and 14% in rainbow trout.

Diagnosis

Clinical

Infectious salmon anemia should be a consideration in Atlantic salmon with increased mortality and signs of anemia, or lesions consistent with this disease. It should always be investigated if the hematocrit is less than 10%.

Differential diagnosis

The differential diagnoses for infectious salmon anemia include other causes of anemia and hemorrhages, as well as winter ulcer and septicemias caused by *Moritella viscosa*.

Laboratory tests

Outbreaks of infectious salmon anemia can be diagnosed by virus isolation, the detection of antigens and RT-PCR. A few isolates from sick salmon have been difficult to culture, even when viral nucleic acids can be found. The avirulent isolates carried subclinically in wild salmonids can usually be detected only by RT-PCR.

ISAV can be isolated in SHK-1 (Atlantic salmon head kidney) or ASK (Atlantic salmon head kidney leukocyte) cell lines, or in other susceptible lines such as CHSE-214 (Chinook salmon embryo) or TO (Atlantic salmon head kidney leukocyte) cells. All isolates do not grow in all cell lines; if possible, more than one type of cells should be inoculated. A few strains, including a Chilean Atlantic salmon isolate and some North American ISAV isolates, can grow in the EPC (Epithelioma papulosum cyprini) cell line, a non-salmonid cell line that was not previously thought to be permissive to ISAV. Cytopathic effects (CPE) are more apparent in some cell lines than others. The identity of the virus can be confirmed by RT-PCR, immunofluorescence, hemadsorption or other assays to detect viral antigens and nucleic acids.

Viral antigens can be detected in tissues or cell cultures with an indirect fluorescent antibody (IFA) test. Antigens can also be detected in tissues by immunohistochemistry. Rapid kits based on immunochromatography are available in some countries. RT-PCR is usually used to detect nucleic acids in tissues, but *in situ* hybridization has also been employed.

Fish, including Atlantic salmon and rainbow trout, can have humoral responses to ISAV. Enzyme-linked immunosorbent assays (ELISAs) have been developed to detect these antibodies. ELISAs have not been standardized for use in surveillance or the diagnosis of clinical cases;

however, they are occasionally used as supplemental tests in conjunction with other types of assays. Histopathology can also aid in reaching a diagnosis.

Suspect and confirmed cases

The occurrence of noncultivable, apparently avirulent ISA viruses among fish complicates the diagnosis of infectious salmon anemia. There is no gold standard test for ISAV, and the confirmation of infection depends on a combination of test results. The World Organization for Animal Health (OIE) currently defines a suspect case as one that meets any of the following criteria:

- Either clinical signs or lesions are consistent with this disease,
- ISAV has been isolated in cell culture from one sample from a fish
- Two independent tests (e.g., RT-PCR and IFA on tissues) suggest that this virus is present
- Antibodies to the virus have been found

Infectious salmon anemia is confirmed if:

- The illness is consistent with this disease, and
- Viral antigens have been detected in tissues with specific antibodies (e.g., by IFA), and
- The virus has either been cultured or nucleic acids have been detected by RT-PCR from at least one fish.

ISAV infections are confirmed by culturing the virus from at least two independent samples tested on separate occasions. Viral antigens or nucleic acids should be detected in the fish's tissues, on at least one occasion when the virus is recovered.

Samples to collect

Samples should be taken from net pens that contain diseased fish; ISAV may be difficult to detect in adjacent pens, even if very sensitive techniques are used. Because outbreaks are confirmed by using different tests in individual fish (as described above), the OIE does not recommend that these samples be pooled. However, pooled samples may be collected for surveillance by RT-PCR or culture. The number of samples taken for surveillance varies with the prevalence of the virus in the population and the test used.

Blood should be collected for non-lethal sampling. Some authors have also suggested RT-PCR on gill mucus for the screening of live fish. The heart and mid-kidney should be collected for virus isolation and/or RT-PCR. The gills can also be included for surveillance if the RT-PCR test is used; microbial contamination prevents this tissue from being useful for virus isolation. The detection of ISAV in the gills or gill mucus by RT-PCR can be attributed to contamination by viruses in the water rather than to infection.

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Antigens can be found in the kidney, heart and liver using the IFA test. The OIE recommends mid-kidney smears for immunocytochemistry, and the mid-kidney and the heart, including the valves and bulbus arteriosus, for immunohistochemistry. Tissue samples of the mid-kidney, liver, heart, pancreas/intestine, spleen, gills and skin/muscle should be taken for histopathology.

Recommended actions if infectious salmon anemia is suspected

Notification of authorities

Infectious salmon anemia is reportable to the World Organization for Animal Health (OIE). Disease notification requirements for OIE member nations and import/export guidelines can be found in the OIE Aquatic Animal Health Code [<http://www.oie.int/international-standard-setting/aquatic-code/access-online/>]. Veterinarians who encounter a case of infectious salmon anemia should follow their national and/or local guidelines for disease reporting and diagnostic testing.

Notification of authorities in the United States

Infectious salmon anemia should be reported to state or federal authorities immediately upon diagnosis or suspicion of the disease. In the U.S., all active salmonid lease sites must participate in the national surveillance and control program to be eligible for indemnification under this program.

Federal Area Veterinarians in Charge (AVIC):

<https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/contact-us>

State Animal Health Officials (SAHOs):

<http://www.usaha.org/federal-and-state-animal-health>

Control

Good management and biosecurity can decrease the risk of infection. Boat traffic and the movements of fish, supplies and people must be controlled. Boats and equipment should be cleaned and disinfected before and after visiting sites. Well boats (boats that have interior compartments to hold live fish) have especially been linked to the transmission of ISAV between sites. Personnel must also clean and disinfect themselves and their gear. Whenever possible, dedicated equipment and personnel should be used for each site. Divers should disinfect their gear before and after diving, and between cages. It is recommended that cages with the youngest fish be dived first, and cages with the highest mortality dived last. Dead fish should be removed regularly from cages, as ISAV can be transmitted in blood and tissues. Decontaminating wastes, including wastewater, from slaughter facilities and fish processing plants prevents infections from this source.

Salmon farms should be separated by a distance that will not allow the virus to spread readily. This distance may

vary with the location. To reduce the transmission of ISAV from older fish to young fish, sites should be stocked with a single year-class. (Salmon that entered seawater in the same year are considered to be a “year-class.”) Nets should be disinfected between uses. Fallowing between year-classes is also helpful. (Fallowing = leaving a cage or the entire site empty of fish for a period before restocking). Sea lice, which may be involved in transmission, should be controlled, and stress should be minimized. Some studies suggest that cage design might also affect the risk. Commercial ISA vaccines are available in some countries including Canada, but their use is prohibited in the European Union.

If infectious salmon anemia is detected, aggressive depopulation of the affected cages can decrease losses. Early detection by regular surveillance can improve the effectiveness of this technique, as fish can shed ISAV before the mortality rate increases. Most salmon producing countries enforce mandatory depopulation and disinfection of infected cages; however, the specific strategy may vary between countries. For example, some countries may manage infections at the cage or pen level, while others mandate depopulation of the farm. Quarantines and movement controls are used to prevent the virus from spreading to other farms. Fallowing of infected sites helps eliminate viruses that may remain in seawater and/or marine life and fomites in the area.

Because there is still some controversy about the possibility of vertical transmission, some fish industries (including the U.S.) have adopted broodstock screening techniques for ISA. Egg disinfection, which is used to control a variety of fish diseases, would be effective against viruses transmitted on the surface of the egg.

Disinfection

ISAV can be inactivated by a variety of disinfectants including sodium hypochlorite, chloramine-T, chlorine dioxide, iodophors, sodium hydroxide, formic acid, formaldehyde and potassium peroxymonosulfate (Virkon® S (2% solution/10 minutes; followed by water rinse). This virus is also susceptible to ozonated seawater, temperatures greater than 55°C (131°F) for more than 5 minutes, or extremely acid or basic pH (e.g., pH 4 or pH 12 for 24 hours), well as ultraviolet irradiation.

Noncultivable isolates

Nonpathogenic (eg, HPR0) isolates that can be detected only by RT-PCR do not necessarily trigger automatic disease control efforts. The prevalence of these viruses among salmonid and non-salmonid fish, and their potential to generate virulent isolates, is still poorly understood. Their existence could mean that the complete elimination of infectious salmon anemia among sea-raised salmon might be impossible.

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Public Health

There is no indication that ISAV can affect humans. Because this virus is inactivated at body temperatures of 37°C- 40°C (98.6-104°F), it is unlikely to infect any mammal or bird.

Internet Resources

Canadian Food Inspection Agency (CFIA). Aquatic Animals
<http://www.inspection.gc.ca/english/anima/aqua/aquae.shtml>

CFIA. Infectious Salmon Anemia
<http://www.inspection.gc.ca/english/anima/aqua/infect/infectqueste.shtml>

The Merck Veterinary Manual
<http://www.merckvetmanual.com>

United States Department of Agriculture (USDA) APHIS. Aquaculture
https://www.aphis.usda.gov/aphis/ourfocus/wildlifedamage/operational-activities/sa_aquaculture/ct_aquaculture_index

USDA Infectious Salmon Anemia Program Standards
http://www.aphis.usda.gov/animal_health/animal_dis_spec/aquaculture/downloads/isa_standards.pdf

World Organization for Animal Health (OIE)
<http://www.oie.int>

OIE Manual of Diagnostic Tests for Aquatic Animals
<http://www.oie.int/international-standard-setting/aquatic-manual/access-online/>

OIE Aquatic Animal Health Code
<http://www.oie.int/international-standard-setting/aquatic-code/access-online/>

University of Maine Cooperative Extension
<http://www.umaine.edu/livestock/Publications/isa.htm>

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