**Clinical Guide to Fish Medicine (Hadfield/Clayton, 2021) Chapter A13 Environmental Considerations of Immersion Medications pg. 272 (Diving or swimming in medicated water) – 281**

* Diving or Swimming in Medicated Water
  + diver = humans breathing compressed gases from SCUBA, breathing surface-supplied air, snorkeling, or swimming
  + consider potential known and unknown human health and safety hazards for divers regarding medications in the water
    - primary compound chemical and breakdown chemicals
    - historically calculated human safe dose if ingested
      * doesn’t consider route of exposure
    - consult Safety Data Sheets (SDS)
  + medicated water = “polluted” water
    - EPA polluted water definition: water that could make a diver sick (now or later), increase a diver’s risk of developing cancer, or cause any undesirable outcome for diver, tender, or other persons that may have contact
  + OSHA - no specific regulations for chemicals encountered as immersion therapeutics but regulatory oversight through General Duty clause (OSHA section 5)
  + US federal General Industry Standards Hazardous Waste Operations and Emergency Response (29 CFR 1910.120) requires development of written health and safety programs which provide standard operating procedures and site-specific health and safety plans
    - plan for diver health and safety
      * only suitably trained staff should be diving
      * assessment of hazards associated with chemotherapeutic agent
      * PPE
      * specific and detailed work plan
      * diver decontamination plan
      * methods to determine when normal operations are safe to resume
  + primary routes of exposure for diver - inhalation, ingestion, skin contact
    - inhalation, ingestion - prevented by utilizing full face masks/helmets with positive pressure and redundant breathing system
      * avoid mouth piece regulators
    - vulcanized rubber hazmat dry suit with attached boots, dry gloves, protective gauntlet mitigate skin contact
      * avoid neoprene wetsuits
    - rinse station when exiting water to remove and discharge the medicated water
  + decision on when to resume normal dive operations depends on medication, method for management of medicated water, type of system treated, specific treatment protocol
    - gold standard - assays of parent compound in water as objective data to guide decision
    - Systems with substrate, especially carbonate-bearing substrate (e.g. crushed coral), artificial rockwork, and/or other tank furnishings, can accumulate chemicals within these materials
  + Disposal of Medicated Water
    - 5 basic methods for disposal:
      * Discharge to municipal sanitary sewer
        + Most common in aquariums
        + Not inexpensive
        + Not necessarily environmentally safe
        + communities in areas with little annual rainfall reluctant to accept seawater
        + avoid direct contamination of natural bodies of water
        + routine wastewater treatment increases opportunity for biotic or abiotic breakdown of some chemotherapeutics
        + medications not removed by routine wastewater treatment facilities - fenbendazole, estrogens
      * Discharge to a natural body of water
        + easiest and cheapest method
        + environmental, public health, and ethical problems associated with open discharge
        + bioaccumulation of chemicals in animals, plants, and sediments
        + widespread contamination downstream and groundwater
        + salt water into freshwater bodies - significant ecological impacts 🡪 decreased biodiversity, changes in natural character of aquatic ecosystems, lower productivity
        + increasing antibiotic resistance in aquatic environments
        + regulated at multiple levels in most locations
      * Return to the institution’s water system
        + inexpensive and easy
        + environmental, public health, and ethical concerns not as great as above
        + possible widespread impacts on animals and plants within the institution and critical biological filtration
        + possible bioaccumulation in living organisms
        + medications may bind to objects and environment and leach out in future
        + often not recommended
      * Biotic or abiotic removal or destruction of the compound
        + use natural (biotic) or physical (abiotic) methods to remove the drugs from the water
        + most effective when water levels of agent can be measured
        + some methods may result in breakdown of parent compound into different chemicals
        + less convenient and more expensive than immediate discharge
        + Biotic elimination effective for praziquantel
        + Common abiotic methods include adsorption, photolysis, oxidation, reduction

activated carbon effective at removing many organic compounds including formalin, trichlorfon, chloroquine, praziquantel

carbon - adsorption process mechanically binds compound and does not alter or eliminate it

inorganic copper poorly adsorbed unless bound to organics

zeolite – may be effective in removing immersion drugs from water

selective

may alter parent compound into one or more unknown chemicals

expensive

UV light

Ex) praziquantel, chloroquine, tetracycline, oxytetracycline

may result in toxic by-products

Ozone - effective at degrading organic compounds, ozone and other potent oxidizers can react with compounds to create toxic by-products

* + - * + Nanofiltration and ultrafiltration methods

molecular size and water solubility influence ability of nanofiltration and ultrafiltration membranes to remove dissolved compounds from water

* + - * Transfer to evaporation pond with subsequent removal of sludge
        + Less common
        + shallow, artificial ponds with a large surface area that enhances water evaporation by sunlight and high temperatures
        + pollutants accumulating in either crystalline or concentrated sludge form
        + sludge require proper handling, treatment, and disposal
        + evaporation ponds - lined or unlined

lined ponds - use synthetic liners to contain liquid, alarm system to detect leaks, no impact on groundwater

unlined ponds - substrate materials compacted and consist of soil with very low permeability

* + - * + ponds must include fencing and nets to avoid wildlife and humans accessing water
        + expensive
  + Record-Keeping
    - regulatory and accreditation standards, require proper documentation of all drug prescriptions, including immersion medications, within the veterinarian–client–patient relationship
  + Drug Examples
    - Formalin
      * 37% formaldehyde gas (CH2O) dissolved in water, with 10–15% methanol
      * used commonly to treat ectoparasites and oomycetes
      * unpredictability - can cause rapid decrease in dissolved oxygen, most pronounced in systems with algae and limited gas exchange
      * formalin can combine with organic matter in system, reducing its treatment efficacy
      * can become more toxic at higher water temperature
        + should not be used in water >27°C (80°F)
      * more toxic in soft, low-pH water
      * rapidly degraded by bacteria within microbiome
      * paraformaldehyde - highly toxic by-product that can develop, particularly following exposure to temperature extremes
      * indirectly decreases oxygen by rapidly killing algae and phytoplankton
      * increased aeration during treatment and dissolved oxygen should be monitored
      * increased ammonia possible
      * Bioassays - strongly recommended prior to treatment of a new species or high concentration baths
      * formalin toxicity in fish reported although environmental conditions must be considered
        + susceptible groups - some scaleless fish and elasmobranchs
        + signs of toxicity - dyspnea, tachypnea, pallor, excess mucous, erratic swimming, inappetence, and death, often in 24–48 hrs
        + toxic to many invertebrates, algae, and vascular plants
        + toxicity increases with increasing water temperature and decreasing pH
        + higher doses can damage biological filtration
      * formaldehyde shows rapid degradation in water, aeration also shown to increase formalin degradation in aquaria
    - Trichlorfon
      * used to treat copepods, branchiurans, leeches, and monogeneans
      * Unpredictability - concentration and effectiveness of trichlorfon can depend on source, carrier, age, and exposure
      * Avoid mixing with other therapeutics as it could result in dangerous by-products
      * very susceptible to microbial digestion
        + can increase over time 🡪 not to be used routinely as prophylactic
      * Dichlorvos - major transformation product of trichlorfon
        + 100+ times more toxic than trichlorfon
        + increases with increasing alkalinity and increasing temperature
      * rapidly formed by hydrolysis in water, can also be formed by photolysis
      * primary mode of action - inhibition of enzyme cholinesterase that breaks down acetylcholine 🡪 accumulation of acetylcholine 🡪 disruptions in CNS
      * moderately toxic to most fish, particularly elasmobranchs, and highly toxic to invertebrates and waterfowl
        + hyperactivity, tremors, seizures, and death, leukopenia, anemia
      * bioaccumulation - low because of low persistence in water and hydrophilic properties; it tends to remain in water and not in sediment or suspended solids
      * does not typically interfere with biological filtration
      * readily water-soluble and will not discolor the water
      * decrease in oxygen or increase in ammonia may occur
      * bioassays essential due to toxicity of trichlorfon and its unpredictable transformation to exponentially more toxic by-product (dichlorvos)
      * particularly hazardous due to transdermal absorption
      * considered hazardous waste
    - Praziquantel
      * immersion often used for monogeneans, activity against digenes, cestodes, and acanthocephalans
      * Unpredictability - lipophilic and dissolves poorly in water
      * 2 methods used to improve dissolution - manually dissolved into aquarium water or dissolved in just enough 95% ethyl alcohol to form a thick paste
      * can be irritating to fish gills and may result in potentially fatal gill damage if not dissolved well
      * rate of decomposition affected by temperature and light exposure
      * rapid degradation by microbial community of aquatic system
      * wide safety index for fish and plants
      * effect on monogeneans reduced for parasites that reside deep within the gill lamellae, protected by gill inflammation, or are encapsulated as ova
      * does not typically interfere with biological filtration
      * no effect on dissolved oxygen, alkalinity, pH, turbidity, or color
      * bioassay testing a small cohort of individuals is advised with new species although less crucial
      * levels reduced using granular activated carbon treatment, ozone, or UV, but rapidly degraded by bacteria
    - Copper Sulfate, Chelated Copper
      * Organic copper salts - chelated copper and copper citrate
      * treat ectoparasites (particularly Cryptocaryon spp.) and oomycetes
      * also used as an algaecide and to eradicate snails
      * therapeutic range depends on salinity, alkalinity, product, and parasite
      * high temperatures, low alkalinity, and low pH increase risk of toxicity by increasing proportion of ionic copper and uptake of copper by fish
        + treatment regimens are different in salt water compared to freshwater
      * copper more readily precipitates out at higher alkalinities and binds to calcareous materials (dolomite, crushed coral, oyster shell) affecting level of copper in solution
      * bacteria exponentially increase uptake rate during treatment
      * may be acutely toxic to some species of finfish, most elasmobranchs, and most invertebrates
      * increased toxicity in older fish and increased toxicity in juveniles
      * directly toxic to variety of tissues and damage to immune system can increase risk of secondary disease
      * Signs of toxicity - inappetence, changes in coloration, lethargy, and acute mortalities
      * slow increase to reach therapeutic concentration recommended
      * can be toxic to algae and vascular plants
      * inhibitory effect on biological filtration, particularly following rapid dosing
      * ammonia-binding compounds cannot be used with copper since they will increase copper toxicity by reducing Cu2+ to Cu+
      * does not cause turbidity or discoloration of water but can cause an increase in ammonia and nitrite due to inhibition of nitrifying bacteria
      * bioassay on small cohort of individuals and conservative dosing are advised with new species or life stages
      * activated carbon and water changes typically used to remove copper
    - Chloroquine diphosphate
      * treat external protozoa such as Cryptocaryon irritans, Amyloodinium ocellatum, trichodinids, and scuticociliates
      * increased toxicity seen with increasing pH
      * stable in aquatic systems
      * readily degraded by UV light
      * reduce bioavailability of praziquantel in rats and humans
      * can be toxic to some invertebrates and algae
      * inhibitory effect on biological filtration, either directly or indirectly, particularly at high doses
      * increase in ammonia and nitrite due to inhibition of nitrifying bacteria
        + increased ammonia and decreased dissolved oxygen
      * repeated treatments of chloroquine diphosphate with limited water turnover may increase phosphate level in water
      * bioassay by testing a small cohort of individuals is always advised with new species

**Clinical Guide to Fish Medicine (Hadfield/Clayton, 2021) Chapter C3 Viral Diseases pg. 425-430**

* Megalocytiviruses
  + infectious spleen and kidney necrosis virus (ISKNV)
  + scale drop disease virus (SDDV)
  + pathogens of freshwater and marine teleosts
  + Family Iridoviridae, Genus Megalocytivirus
  + large, enveloped or non-enveloped DNA viruses
  + transmission - horizontal reported, vertical suspected
  + Risk Factors: permissive water temperature varies (RSIV causes morbidity in rock bream at 18–30°C (64–86°F) but not at <13C (55F)
  + no known zoonotic potential
  + Signs/Clinical Findings
    - Asymptomatic
    - Lethargy, abnormal swimming, or abnormal position in water column, inappetence, skin darkening or pallor, petechiae, erythema, ulcers, or other skin lesions, scale loss common with SDDV, exophthalmos, dyspnea or tachypnea, gill pallor due to anemia common with RSIV, gill petechiae, white feces, coelomic distension due to effusion
    - mortality can vary from 0-100%
  + Diagnosis - characteristic inclusions on histology and virus isolation or PCR
  + clinical pathology - possibly hemolytic anemia; erythrocytes may show large eosinophilic intracytoplasmic inclusion bodies
  + Necropsy - pallor, petechiae, splenomegaly, renomegaly, hepatomegaly, and serosanguinous coelomic effusion, necrosis and inflammation with large, disseminated mesenchymal cells with high cytoplasm to nuclear ratios and large, basophilic or amphophilic intracytoplasmic inclusions
  + spleen and kidney most commonly affected
  + Inclusions less common with SDDV
  + RSIV reportable
* Orthomyxoviruses
  + infectious salmon anemia virus (ISAV)
    - most common
    - severe hemolytic anemia in Atlantic salmon
    - Family Orthomyxoviridae, genus Isavirus
    - enveloped RNA viruses
    - transmission - horizontal reported, vertical suspected
    - virus only survive for hours to days in seawater
    - vectors probably include sea lice
    - carriers - brown trout, pollock, and Atlantic cod
    - lifelong immunity and resistant to reinfection
    - natural infection seems limited to Atlantic salmon, mostly in salt water
    - all life stages susceptible
    - risk factors - permisssive water temperature often ~15°C (59°F) with no viral replication at 25°C (77°F)
    - Signs/Clinical Findings - typically chronic, multiple Atlantic salmon usually affected, lethargy common, usually in good condition, tachypnea, dyspnea, gill pallor common due to severe anemia, exophthalmos, hyphema, or coelomic distension
    - daily mortality rate usually low with cumulative mortality typically <50%
    - DDX anemia and hemorrhages in Atlantic salmon - ISAV, erythrocytic inclusion body syndrome, infectious hematopoietic necrosis virus, infectious pancreatic necrosis virus, Moritella viscosa, Yersinia ruckeri, cardiomyopathy syndrome
    - Diagnosis - virus isolation and PCR
    - Clinical path- severe anemia with PCV <10% in late stage
    - Necropsy -visceral pallor, coelomic effusion, renomegaly, splenomegaly, or hepatomegaly with necrosis, petechiae, and hemorrhages
    - ISAV reportable to OIE
    - Treatment - nucleotide analog ribavirin PO 6.5μmol/kg SID for 10 days reduced mortality of experimentally infected salmon
    - Prevention –
      * Atlantic salmon sea pens kept far from wild stocks, other farmed Atlantic salmon (>5km), and salmon processing plants
      * USDA-approved vaccine available, protection variable
* Betanodaviruses
  + marine teleosts.
  + vacuolating encephalopathy and retinopathy (VER) or viral nervous necrosis (VNN)
  + vacuolar lesions in brain and retina
  + risk to global aquaculture, particularly Mediterranean mariculture
  + Family Nodaviridae, genus Betanodavirus
  + viruses typically identified based on common name followed by nervous necrosis virus (NNV)
  + 4 species recognized by International Committee on Taxonomy of Viruses
    - Striped jack NNV
    - Tiger puffer NNV
    - Red-spotted grouper NNV
    - Barfin flounder NNV
  + small, non-enveloped RNA viruses with icosahedral capsids
  + transmission - horizontal reported, vertical likely in some species
  + viruses can survive freezing and extended periods in saltwater, particularly at low temps
  + invertebrate vectors reported (Manila clams for red-spotted grouper NNV)
  + viruses found in common live feeds such as brine shrimp (Artemia) and copepods
  + carriers - gilthead sea bream and other species
  + Signs/Clinical Findings
    - multiple conspecifics usually affected
    - typically acute
    - abnormal swimming often predominant sign (spiraling, darting, or inverted swimming)
    - flatfish may be recumbent on wrong side
    - inappetence, apparent blindness, progressive changes in coloration
    - mortality may reach 100%
  + common DDX for neurologic signs in multiple bony fish - bacterial, viral, and toxic etiologies
  + diagnosis - histology of CNS
    - histology - vacuolating necrosis of neural cells of spinal cord, brain, and retina, intracytoplasmic inclusion bodies may be seen
    - TEM can show shape of virions
    - combination of histology, RT-PCR, virus isolation, and sequencing
  + disinfection
    - Nodaviruses relatively resistant to UV
    - Nodaviruses variable response to ozone disinfection, often needing high doses
    - routine chemical disinfectants may need higher doses or longer contact times
    - prolonged drying is helpful (>7 days)
  + no antiviral treatments reported, but supportive care may be helpful

*J Aquat Anim Health* 2017 29(4):214-224

[**Susceptibility of Representative Great Lakes Fish Species to the North Carolina Strain of Spring Viremia of Carp Virus (SVCV)**](https://doi.org/10.1080/08997659.2017.1360410)

Boonthai T, Loch TP, Standish I, Faisal M

**ABSTRACT:** Spring viremia of carp virus (SVCV) is a notifiable pathogen of the World Organization of Animal Health. Since SVCV was isolated in Lake Ontario in 2007, concern has grown about its spread in the Great Lakes basin and its potential negative impacts on fish species of importance in stock enhancement programs basinwide. The susceptibility of representative fish species from the families Cyprinidae (Fathead Minnow *Pimephales promelas,* Golden Shiner *Notemigonus crysoleucas*, Spotfin Shiner *Cyprinella spiloptera*, and Creek Chub *Semotilus atromaculatus*), Centrarchidae (Largemouth Bass *Micropterus salmoides)*, Percidae (Walleye *Sander vitreus*), Salmonidae (Rainbow Trout *Oncorhynchus mykiss*), and Esocidae (Muskellunge *Esox masquinongy*) to SVCV was evaluated by experimental infection under laboratory conditions. Morbidity and mortality were recorded, and virus re-isolation, semi-nested reverse transcription PCR, and histopathological assessments were performed. Using intraperitoneal (i.p.) injection, Fathead Minnows and Golden Shiners were highly susceptible to SVCV (40-70% mortality). All dead or moribund and apparently healthy surviving Fathead Minnows and Golden Shiners were SVCV positive. The SVCV was also detected in challenged but healthy Spotfin Shiners (30%) and Creek Chub (5%). However, noncyprinid species exhibited no morbidity or mortality and were free of SVCV following an observation period of 30 d. In a follow-up experimental challenge, Fathead Minnows and Golden Shiners were SVCV challenged at 103 and 105 PFU/mL by means of waterborne immersion. After immersion, Fathead Minnows and Golden Shiners exhibited characteristic SVCV disease signs, but mortality was less (30% and 10% mortality, respectively) than that in fish with i.p. injections. The SVCV was detected in all mortalities and a subset of healthy Fathead Minnows and Golden Shiners. Necrotic changes were observed in the kidneys, liver, spleen, ovaries, and heart, and other histopathological lesions also occurred. These findings suggest that two of the four cyprinids tested are susceptible to SVCV-induced disease and that all four can act as potential carriers of SVCV in the Laurentian Great Lakes

**Study Design**:

* Four non-cyprinid species (Eagle Lake Rainbow Trout, Walleye, Largemouth Bass, and Muskellunge) and four cyprinid species (Spotfin Shiners, Creek Chub, Fathead Minnows, Golden Shiners) were included
  + Fish were first screened for their susceptibility to SVCV using IP injection of either a high dose of SVCV, low dose of SVCV, or sterile saline
* Fathead Minnows and Golden Shiners were chosen to confirm their susceptibility to SVCV using waterborne immersion infection
  + Fish were exposed to either a high dose of SVCV, low dose of SVCV, or sterile saline by immersion for 1 hour
* Virus re-isolation, semi-nested reverse transcription PCR, and histopathological assessments were performed

**Goal:**

1. Identify risks posed by SVCV to four non-cyprinid species that are residents to the Great Lakes basin and of importance to regional stock enhancement programs
2. Assessed SVCV susceptibility in four native cyprinids commonly used to feed piscivorous fishes in hatcheries and as bait in recreational fishing

**Key Points:**

* Spring viraemia of carp virus (SVCV) is a negative-sense, single-stranded RNA rhabdovirus
  + Common carp and its colorful ornamental variety, koi, are highly susceptible to SVCV and are considered the primary hosts
* Since 2002, several SVCV outbreaks have been reported in the United States
  + Numerous isolations were made from outbreaks involving Common Carp, koi carp, Emerald Shiners, Bluegills, and Largemouth Bass in North Carolina, Wisconsin, Illinois, Ohio, Minnesota, Washington, and Missouri
  + In 2007 SVCV emerged in the Great Lakes when virus was isolated from Common Carp in Lake Ontario, Ontario
  + Despite its wide host range, SVCV in North America has been associated with outbreaks in only four fish species belonging to two families: Cyprinidae and Centrarchidae
* 61 fish species in the Great Lakes are threatened or endangered
  + As a result, fishery stock enhancement programs have been developed that rely upon stocking of hatchery-raised fish in public waters
  + This results in keeping fish at high stocking densities for a prolonged period
* One species of concern is the Muskellunge, which is fed cyprinid fish in hatcheries and has proven highly susceptible to another rhabdovirus, viral hemorrhagic septicemia virus (VHSV)
  + Additional concern stems from the fact that the Northern Pike E, a close relative of Muskellunge within the family Esocidae, is extremely vulnerable to the pike fry rhabdovirus, a virus that clusters closely with SVCV within the Sprivivirus genus
  + This study demonstrates that Muskellunge may not be vulnerable to SVCV
    - No morbidity or mortality took place after experimental infection and the virus could not be recovered from the internal organs of infected fish
* No morbidity or mortality took place in Walleye or Largemouth Bass
  + However, SVCV was previously isolated from wild Largemouth Bass during an outbreak that involved Largemouth Bass and Bluegills
  + Wild fish in their aquatic habitats are exposed to multitude of stressors and pathogens that may alter their resistance to a certain pathogen
* Reports on the susceptibility of Rainbow Trout to SVCV have been perplexing
  + Rainbow Trout were refractory to experimental infection by a European SVCV strain, but Rainbow Trout fry suffered low to moderate pathogenicity to the North Carolina strain
  + In this study, the Eagle Lake strain of Rainbow Trout was not vulnerable to experimental infection
* SVCV was found to infect each of the four cyprinids, albeit with varying degrees of pathogenicity
  + Spotfin Shiners and Creek Chub did not suffer any morbidity or mortality, but SVCV was isolated from infected individuals
  + Fathead Minnows and Golden Shiners experienced morbidity and mortality after infection and SVCV was isolated from infected individuals
* Behavioral changes and clinical signs of moribund Fathead Minnows and Golden Shiners resemble SVCV in Common Carp
  + However, ecchymotic hemorrhages on the outer swim bladder membrane seen in infected Common Carp were not observed
  + Histopathological lesions included necrotic changes in most organs examined, along with widespread hemorrhages, consistent with those in other SVCV-infected cyprinids

**TLDR:**

* After experimental infection with SVCV, none of the non-cyprinid species (Eagle Lake Rainbow Trout, Walleye, Largemouth Bass, and Muskellunge) experienced any morbidity or mortality
* SVCV was found to infect each of the four cyprinids, albeit with varying degrees of pathogenicity
  + Spotfin Shiners and Creek Chub did not suffer any morbidity or mortality
  + Fathead Minnows and Golden Shiners experienced morbidity and mortality

**Related Articles:** *None on the current ACZM reading list*

# Hadfield/Clayton Chapter C3 Viral Diseases

**Pages 417-424**

**Birnaviruses**

* Non-enveloped double stranded RNA viruses
* Most common = infectious pancreatic necrosis virus (IPNV)
* Important pathogen of young salmonids, particularly rainbow trout
  + Only pathogenic in salmonids
* Causes acute septicemic disease
* No known zoonotic potential
* Transmission
  + Highly contagious via horizontal and vertical transmission
  + Unlike other viruses, IPNV can be carried inside the egg
  + Can survive days to weeks in surface water, months in frozen tissues
  + Mechanical/biological vectors: mollusks, crustaceans, leeches, piscivorous birds
  + Fish that resolve clinical signs likely become persistently infected carriers
* Risk Factors
  + Permissive water temperature is often 10–14°C (50–57°F)
  + High # of salmonid farms within a 10 km radius
* Clinical signs
  + Erratic swimming (e.g., spiraling)
  + Skin darkening or hemorrhages
  + Coelomic distension due to organomegaly or effusion
  + White fecal casts, exophthalmos, gill pallor due to anemia may be seen
  + Appetite is usually normal
* Diagnosis
  + Virus isolation from posterior kidney or pyloric ceca
  + Necropsy or coeliotomy may show tissue pallor and white or clear mucus in the stomach and intestines
  + Histology usually shows pancreatic necrosis and basophilic intracytoplasmic inclusions
    - McKnight cells (karyolitic and necrotic epithelial cells) may be present in the pyloric ceca
    - Other findings include necrosis of anterior intestines and renal tubules
* Management
  + Depopulation and disinfection
    - Birnaviruses are hardy
    - IPNV is resistant to air drying and requires UV doses of 100–330 mJ/cm2
  + Test for IPNV prior to acquisition of young salmonids
  + Acquire salmonids at >6 mo of age
  + Consider disinfection of eggs with iodophors to reduce transmission
    - Does not eliminate it, as IPNV can be carried inside eggs

**Pox Viruses**

* Enveloped double stranded DNA viruses
* Pox viruses are rarely reported in fish
* No known zoonotic potential
* Carp edema virus (CEV) is an emerging pox virus
  + Only infects common carp and subspecies such as koi
  + Also called koi sleepy disease due to the profound lethargy
* Transmission & Epidemiology
  + CEV was first found in Japanese koi breeding facilities in the 1970s
  + International trade in koi likely contributing to its global spread
  + Horizontal transmission
  + Fish that resolve clinical signs may become carriers
    - Fish typically remain PCR-positive for 5-6 months
  + Outbreaks are more common at 15–25°C (59–77°F)
* Clinical Signs:
  + Multiple fish affected; mortality may reach 70-100%.
  + Adult fish show severe lethargy, often laterally recumbent and minimally responsive
    - Younger fish may congregate at the surface or sides of a pond.
  + Hyporexia to anorexia, skin edema, dyspnea/tachypnea
  + Ulcerative or hemorrhagic skin lesions, particularly around the mouth and the base of the fins
  + Pale, edematous gills with white or gray areas of necrosis and enophthalmos, like KHV
* Diagnosis
  + Typically based on clinical signs, histology, and PCR
  + Histology usually shows branchitis with severe epithelial hyperplasia, necrosis, lamellar fusion, interstitial edema, and increased mucus
    - Large intracytoplasmic inclusions are common
  + PCR assays are best on gill tissue from animals early in the disease process
    - Nested PCR and qPCR tests are available experimentally and show higher sensitivity and specificity
* Management
  + Isolate affected animals to reduce transmission
  + Reduce or resolve stressors, in particular adequate dissolved oxygen
  + Increasing salinity to 5g/L can significantly reduce morbidity and mortality
  + Similarly, increase salinity to 5g/L during quarantine of carp or koi
  + Consider PCR testing for CEV prior to carp or koi clearing quarantine

**Lymphocystis disease viruses (LCDVs)**

* Large, enveloped double stranded DNA viruses
* Cause hypertrophy of fibroblastic cells leading to skin plaques or nodules
* Common in tropical and subtropical marine and freshwater teleosts
  + Less common but also reported in temperate teleosts
  + Despite wide host range, many strains seem relatively host-specific
* The disease is a cosmetic concern and an indicator of stressors; rarely cause systemic disease
* These viruses have no known zoonotic potential
* Horizontal or vertical (on egg surfaces) transmission
* Clinical Signs:
  + Asympotmatic
  + White or tan plaques or nodules on skin or fins are typical, particularly on the rostrum, over the operculum, and near the lateral line
  + Morbidity and mortality are low
* Diagnosis
  + Usually based on examination of skin scrapes under direct microscopy
  + Wet mounts show extremely large, round cells with thickened outer membranes
  + Histology shows encapsulated hypertrophied cells w/ NO inflammatory response
  + Feulgen-positive intracytoplasmic inclusion bodies are common
* Management
  + Reduction or resolution of stressors is the most effective management
  + Lesions regress over days to months if stressors are removed
  + Surgical debridement can speed resolution

**Ranaviruses**

* Large enveloped or non-enveloped DNA viruses
* Important emerging pathogens of fish, amphibians, and reptiles
* No known zoonotic potential
* Cause severe inflammatory disease and epizootics in wild and cultured fish
* Epizootic hematopoietic necrosis virus (EHNV) is endemic to Australia
  + Can cause epizootic disease in redfin perch
  + Should not be confused with infectious hematopoietic necrosis virus (IHNV), which is a rhabdovirus
* Taxonomy
  + Wide variety with relatively wide host ranges
  + Fish viruses with "iridovirus" in the name are from the family Iridoviridae
    - However, may be from the genus *Ranavirus* or *Megalocytivirus*
    - The genus *Iridovirus* consists of invertebrate viruses
  + Two amphibian ranaviruses can cause disease in fish: frog virus 3 (FV3) and Bohle iridovirus (BIV)
* Transmission: horizontal common, vertical suspected, fish/amphibians may be carriers
  + Viruses are resistant to drying and can survive for months in water and sediment and > 2 years in frozen fish tissues
  + Host ranges are often wide, almost always in freshwater
  + Permissive water temperatures are often high (e.g., 11–20°C (52–68°F) for EHNV)
* Many of these viruses can be carried asymptomatically or with mild nonspecific signs
  + If signs are seen, they are typically acute and systemic
  + Multiple conspecifics are usually affected
  + Lethargy; skin darkening, petechiae, erythema, skin ulcers, or fin erosions; erratic swimming, spiraling, loss of equilibrium, or floating may be seen
* Diagnosis is typically based on histology and virus isolation
  + Necropsy or coeliotomy findings usually include petechial hemorrhages, splenomegaly, and renomegaly
  + Histology findings consist of systemic, necrotizing inflammation
    - Occasional basophilic, intranuclear inclusion bodies
    - Hematopoietic tissue in the liver, spleen, and cranial kidney are often the worst affected
  + Virus isolation is straightforward
* Management
  + Depopulation and disinfection may be considered if there is significant morbidity and mortality
  + Routine disinfectants at standard doses should be effective
  + Risk assessments are important when sourcing fish from endemic areas (e.g. freshwater fish from Australia)

**Extralabel Drug Use in Wildlife and Game Animals**

Clapham MO, Martin KL, Davis JL, Baynes RE, Lin Z, Vickroy TW, Riviere JE, Tell LA.

JAVMA 2019;255(5):555-568

**Key Points**

* FARAD extralabel drug use (ELDU) regulations under AMDUCA apply to any animal that could enter the human food chain including free-ranging and captive or rehabilitating wildlife.
  + ‘Game animal’ under FDA: from which food products may be derived that’s not classified as livestock
  + Hunted wildlife are considered minor food-producing species
* Primary causes of illegal drug residues in animal-derived food products in the US: failure to observe drug label directions and withdrawal times, human negligence, poor food manufacturing practices
* Animals should not be anesthetized or treated and released during their hunting season
  + If you must: identification is recommended (tag or collar) with a warning not to consume before a specific date or a phone number to call before consuming
* AMDUCA ELDU: drug must be approved by the FDA, used for therapeutic rather than production purposes on the lawful written or oral order of a licensed vet within a valid VCPR
  + If the animal may enter the human food chain: ID the animal, establish an appropriate and substantially extended withdrawal interval, and ensure it is adhered to
  + ‘Tolerance’ - max concentration of marker residue (drug or one of its metabolites) deemed safe for human consumption
  + ELDU in wildlife is only permissible when it can be kept in captivity or otherwise identified as not safe for human consumption during the withdrawal interval
* Yearly FSIS publications: *Blue book* (National Residue Program Residue Sampling Plan) and *Red book* (National Residue Program Residue Sample results from previous years)
* It is illegal for producers, wildlife rehabilitators, or biologists to use a prescription or over-the-counter medication in an extralabel manner unless prescribed or dispensed by a licensed vet within a valid VCPR.

**Medicated** **feeds**: Extralabel use of medicated feeds is prohibited in major food-producing species and **not permitted** in free-ranging wildlife.

**Controlled substance** regulations: US Code of Federal Regulations Title 21 and Controlled Substance Act

* + Even though biologists can get a DEA registration number and legally obtain controlled substances, they cannot administer them to animals without veterinary guidance because controlled substances are available only by prescription and must be used by or on the order of a licensed vet within a valid VCPR

**Indexed drugs**: under Index of Legally Marketed Unapproved New Animal Drugs for Minor Species

* + Undergo alternate FDA review procedure for safety and effectiveness, intended for markets that are too small to support costs of standard FDA drug approval process
  + ELDU of indexed drugs is **prohibited** in all animal species

**Compounded drugs**: any manipulation of a drug beyond what is included on the FDA-approved label, typically viewed as a new drug

* AMDUCA prohibits administration of drugs compounded from bulk substances

**Vaccines**: considered veterinary biologics, regulated by USDA Center for Veterinary Biologics

* Technically AMDUCA does not apply to biologics, extralabel use of vaccines is allowed at the discretion of the veterinarian of record
* Most vaccines marketed for food animals in the US have a 21-day slaughter withdrawal period

**Hormones**: Extralabel use under AMDUCA (implants for therapeutic purposes only, not management)

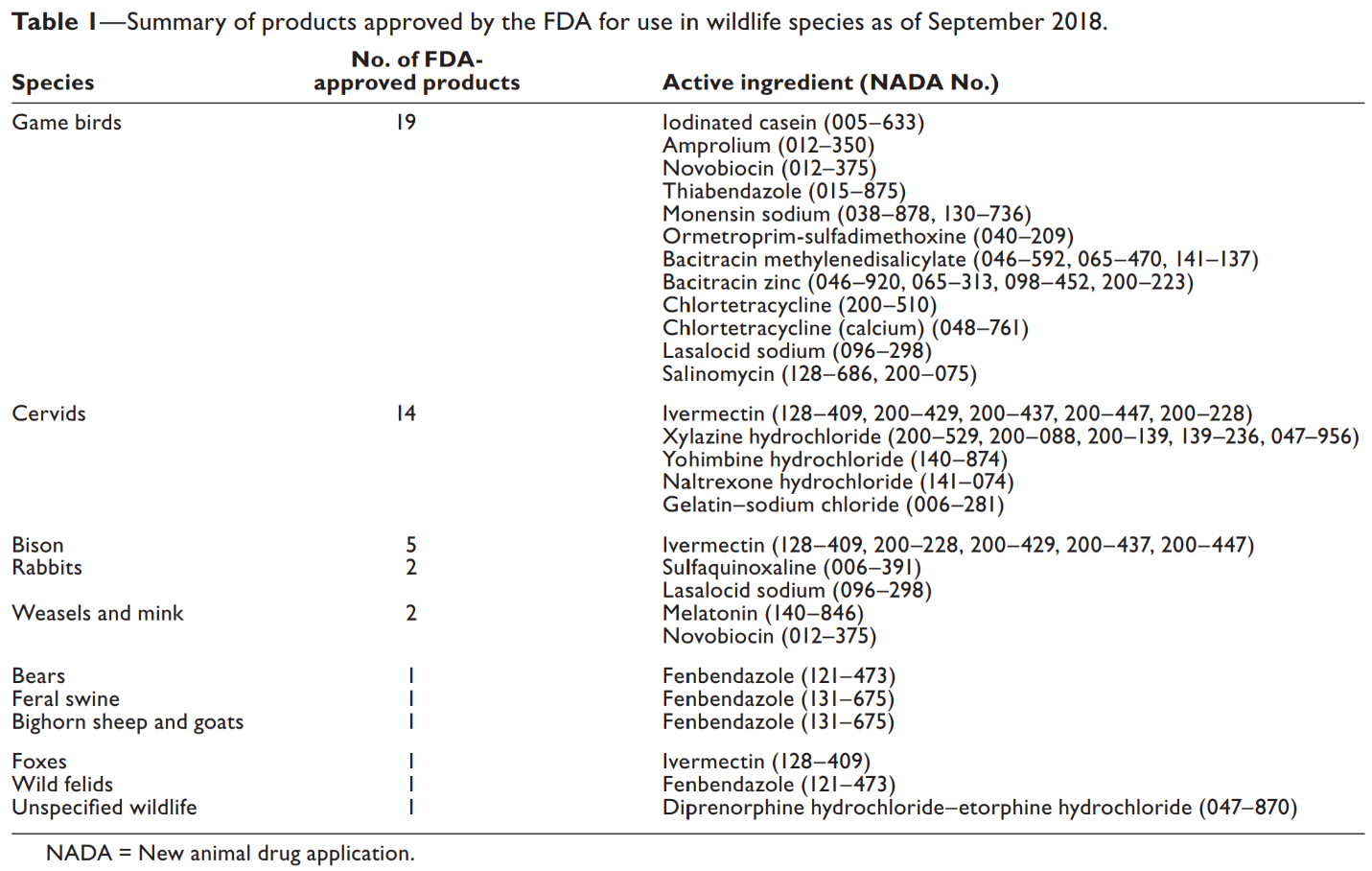
* Most implants with a naturally occurring hormone have a 0-day withdrawal time when administered in accordance with the FDA-approved label

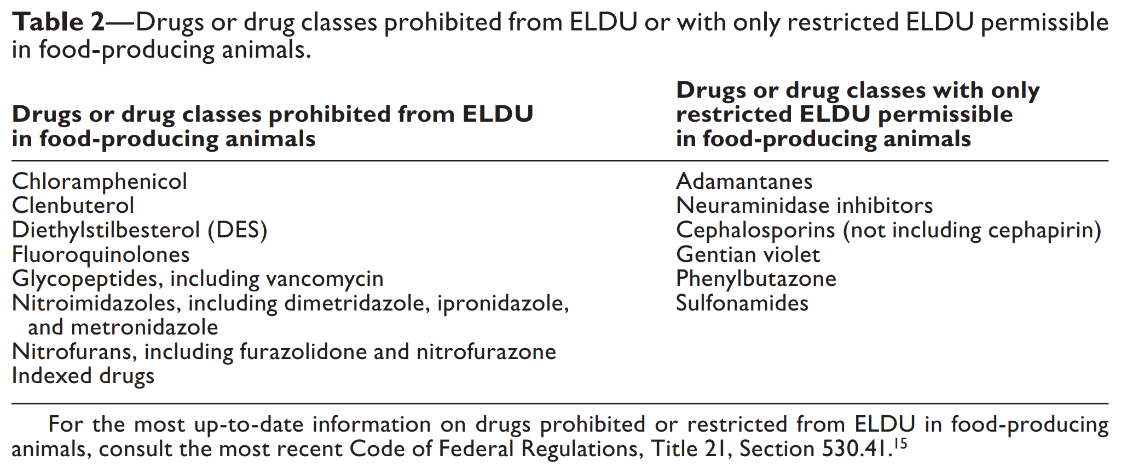
**Analgesics/Anesthetics**: Remote drug delivery can cause more muscle damage and necrosis which can cause prolonged or erratic drug elimination and withdrawal interval is generally longer than the same drug administered IM with hand-held syringe.

* Pharmacological antagonists: compete for or alter receptor sites and displace agonist
* Physiologic antagonists: oppose pharmacological effects by acting on different receptors

**In the US it is illegal for drugs prohibited or restricted in food animals by the FDA to be administered to any animal, domestic or wild, that could potentially enter the human food chain.**

* Ie. Enrofloxacin - labeled only for respiratory disease in swine at any age and beef and dairy cattle < 20 mo, and for colibacillosis in weaned pigs



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**Conclusions**

* In the absence of an established tolerance for a particular drug in a species, detection of that drug or any metabolite in edible tissue is considered a violation and subject to regulatory action
* FARAD recommends prolonged withdrawal intervals after ELDU in wildlife and game species
* Avoid anesthetizing or treating and releasing animals into native habitats during hunting season
* If it cannot be avoided, identify the animal in some manner to alert hunters

**Clinical Fish Medicine Ch A12 Medical Treatment**

Commonly used Medical Treatments

**Antibiotics**

* Few antibiotics approved by US FDA for use in fish: florfenicol, sulfadimethoxine-ormetoprim, sulfamerazine, oxytetracycline \*approved for specific products, taxa, and indications
* All antibiotic use in ornamental fish is considered extra-label in the US

Amikacin - concentration-dependent, bactericidal aminoglycoside

* Gram negative bacteria, some in vitro effect piscine mycobacteriosis
* Parenteral only, doses are empirical

Cefovecin - time-dependent, bactericidal third-gen cephalosporin

* Gram-negative bacteria
* Parenteral only, interindividual variation in plasma concentrations

Ceftazidime - time-dependent, bactericidal third-gen cephalosporin

* Gram negative bacteria, esp *Pseudomonas* spp.
* Parenteral only, PK in koi

Ceftiofur - time-dependent, bactericidal third-gen cephalosporin

* Gram-negative, some Gram-positive B-lactamase producing bacteria
* Parenteral only
* Minor adverse effects: avascular necrosis at IM injection site, resolved spontaneously

Enrofloxacin - bactericidal, concentration-dependent second-gen fluoroquinolone

* Gram-negative and Gram-positive bacteria
* Conversion to active metabolite ciprofloxacin varies across species but often low
* Oral has lower peak plasma concentrations but longer half-life possibly from entero-hepatic cycling (less frequent but higher doses recommended for oral compared to parenteral)
* IM: local skin discoloration, muscle hemorrhage, inflammation, necrosis
* Intracoelomic: dilute 50:50 with sterile saline due to low pH
* Immersion: higher doses in seawater than freshwater because fluoroquinolones complex with divalent cations; can damage ammonia-oxidizing bacteria in biological filtration
* Caution in juvenile fish, spinal deformities reported

Ciprofloxacin - bactericidal, concentration-dependent second-gen fluoroquinolone

* Gram negative and Gram-positive bacteria
* Required doses may be higher than for enrofloxacin because of lower bioavailability

Oxolinic Acid - bactericidal, concentration-dependent quinolone

* Gram-negative
* Approved for use in aquaculture fish in Europe
* Immersion most common in practice: better absorbed in soft water and at low pH because divalent cations chelate quinolones (higher doses recommended in hard water)
* Short half-life and frequent dosing may be required

Azithromycin - bactericidal, concentration-dependent macrolide

* Some gram-negative and gram-positive bacteria, some *Chlamydia* activity

Erythromycin - bacteriostatic time-dependent macrolide

* Gram-positive bacteria, *Renibacterium*, *Streptococcus*, prokinetic for upper GI
* Phosphate and stearate forms best for bioencapsulation in brine shrimp
* Immersion can damage biological filtration

Florfenicol - bacteriostatic, time-dependent

* Gram-negative and some gram-positive (*Streptococcus*)
* As of 2019, florfenicol is approved in the US for *Edwardsiella ictaluri*, *Flavobacterium columnare, Flavobacterium psychrophilum, Aeromonas salmonicida, Streptococcus iniae* in catfish and freshwater-reared finfish; 15 day withdrawal; must be used under veterinary feed directive (VFD)
* High therapeutic margin

Oxytetracycline - bacteriostatic, concentration-dependent tetracycline

* Gram-positive, gram-negative (resistant common), some *Chlamydia* activity
* As of 2019, oxytetracycline dihydrate is approved in the US for specific bacterial diseases in catfish and salmonids with a 21-day withdrawal (Terramycin 200 For Fish)
* Oral bioavailability is low in common carp and European bass causing high fecal residues
* Divalent cations chelate oxytetracycline, little of the drug is active in seawater, calcium and hardness should be kept low; light-sensitive (darkens on exposure)
* High therapeutic index at low water temps but mortality increased over 20C
* Degradation products may be toxic to humans, gloves recommended
* Immersion may affect biological filtration

Nitrofurans (nitrofurazone, furazolidone) - \*Carcinogenic\* and under high regulatory priority by the US FDA; use should be avoided in fish

Sulfamerazine - bacteriostatic sulfonamide

* Approved by the FDA in the 1960s for use in food fish but no longer available in the US

Sulfadimethoxine-Ormetoprim - bacteriostatic potentiated sulfonamide

* Gram-negative and gram-positive bacteria, resistance common, some anticoccidial effects
* As of 2019, Sulfa-Ormetoprim is FDA-approved in the US for *Edwardsiella ictaluri* and *Aeromonas salmonicida* in catfish and salmonids; 3-42 day withdrawal
* Usually PO and bioencapsulated into live prey
* Rectal prolapses reported in cownose rays with coccidia treated at 50 mg/kg PO

Trimethoprim-Sulfamethoxazole - bacteriostatic potentiated sulfonamide

* Gram-negative, gram positive except enterococci
* Higher doses may be needed in freshwater compared to salt water

Trimethoprim-Sulfadiazine - bacteriostatic potentiated sulfonamide

* Gram-negative and gram-positive
* As of 2019, approved for salmonids in Canada and Europe
* Elimination half-life higher with multiple-doses, dosing intervals may need to be extended over time

**Antiparasitics**

Chitin Synthase Inhibitors: Can affect nontarget crustaceans and other invertebrates

Diflubenzuron - chitin synthase inhibitor: crustacean parasites (branchiurans and copepods)

* Active during parasite ecdysis, frequency adapted to life cycle in current environment
* Persistent in the environment, half-life 9 days in freshwater, organic matter contribute to degradation
* EPA permit is required to purchase and use diflubenzuron in the US, must follow label instructions

Lufenuron - chitin synthase inhibitor: crustacean parasites (branchiurans and copepods in ornamental fish), some antifungal activity

* Persists in the environment, light can increase rate of degradation
* Anecdotal toxicity to echinoderms

**Oxidants**

Copper - ectoparasites (esp *Cryptocaryon* spp.) and oomycetes (water mold), kills algae and snails

* Commonly used in quarantine of marine teleosts
* Ionic copper sulfate pentahydrate (bluestone) or chelated copper (copper citrate, EDTA, or ethanolamine; Coppersafe)
* Copper sulfate form - lower applied dose, more ionic copper is available
* Minimize toxicity: fully dissolve prior to use, administer doses slowly and uniformly (can dilute and administer over several hours via a drip system)
* Copper ions readily form salts that are inactive (copper chloride, carbonate) - reduced pH will rapidly release toxic copper ions, sometimes long after treatment was stopped
  + Acute copper toxicity increases when alkalinity or hardness decrease
  + Copper is contraindicated in poorly buffered water (alkalinity <50 mg/L)
* In salt water - target free copper ion concentration is 0.15-0.22 mg/L redosed PRN to maintain therapeutic levels for 14-30 day
* Dose calculations based on copper sulfate having 25.5% active copper ions
* Conservative dosing is recommended, use 5-7 days to reach therapeutic concentrations, measure copper ion concentrations q12-24h throughout and following treatment
  + Colorimetric assays are less accurate than benchtop colorimeter or spectrophotometer
* Copper sulfate can be removed with water changes and activated carbon filtration but removal of chelated copper relies on water changes because it does not adsorb well to carbon
  + Chelated copper in salt water has higher total copper target concentrations
* Copper treatment is less common in freshwater but can be a useful alternative to formalin in aquaculture pond systems
  + Alkalinity should be >50 mg/L
  + Algicidal activity could precipitate a drop in dissolved oxygen, avoid use in ponds with heavy algal growth
    - If you have to use it, split total dose into four and treat each quadrant of the pond at separate times while monitoring dissolved oxygen closely
  + In freshwater, active component is copper sulfate molecule so dose calculations are based on product being 100% active
    - Reacts with carbonates in water to form inactive copper carbonate so target concentration is based on alkalinity (usually 1% of alkalinity) but lower doses may be effective
  + Typically redosed based on parasite life cycle (ig. Q48h for 4 doses for *Ichthyophthirius*)
* Toxic to most elasmobranchs, some teleosts, and most invertebrates
  + Signs of copper toxicity: acute mortality without clinical signs or brief (24h) period of reduced feeding, change in coloration, or increased hiding prior to acute mortality
  + Also mortality through immune suppression
  + Stop therapy immediately
* Toxic to vascular plants, algae, and phytoplankton
* For *Cryptocaryon* spp. In coral systems - best option is to remove susceptible teleosts and treat in isolated system
* For *Cryptocaryon* spp. in systems with teleosts and elasmobranchs - best option may be to remove elasmos while the system is treated
* Copper immersion can damage biological filtration depending on oxidizing bacteria present and prior exposure but his is rare
* Anecdotal reports of insoluble copper wire particles used to treat *Eimeria southwelli* in cownose rays

Chloramine-T - chlorinated and deprotonated sulfonamide: nonselective disinfectant, external bacteria and protozoa in fish

* As of 2019, approved in the US for *Flavobacterium* spp. In freshwater-reared salmonids, walleye, and warm-water finfish; 0-day withdrawal
* 100% active, used as immersion; when dissolved in water, forms hypochlorous acid (strong disinfectant) and hypochlorite ion (weak disinfectant)
  + More active at low pH
* Safer than chlorine because it does not form trihalomethanes with organic matter
* Toxicity has been reported: dyspnea, tachypnea

Formalin - ectoparasites and oomycetes in bony fish

* As of 2019, formalin is approved in the US to treat specific external protozoa and monogeneans in finfish and oomycetes in freshwater finfish and their eggs; 0-day withdrawal
* In the US available over-the-counter without prescription
* Use in fish is banned in the EU because it is a potential carcinogen
  + PPE: goggles and gloves
* Typically 37% formaldehyde, 10-15% methanol, water: considered 100% active
* Immersion decreases dissolved oxygen concentration - always provide additional aeration or oxygenation
* Toxic to some fish: scaleless fish and fry, mortality increases with increased dose
  + More toxic in acidic soft water and at high water temps
  + Dyspnea, tachypnea, lethargy, erratic swimming, acute mortalities up to 48 hours after treatment, gill lesions
* NOT used in elasmos, toxic to algae, vascular plants, and most invertebrates
  + Algal die-off can cause catastrophic drop in dissolved oxygen
* Can be rapidly aerosolized or degraded by microbial flora esp with prior exposure
  + Repeated treatments will often fall below therapeutic level
  + Fish density does not affect rate of formalin degradation
* Can affect biological filtration
  + Artifactually increases ammonia concentration measured with Nessler method
  + NEVER mix with potassium permanganate: could result in fire or explosion
  + Store above 4C in the dark to prevent formaldehyde precipitation which is toxic to fish

Hydrogen Peroxide - oxidizing agent: external Gram-neg bacteria, fungi, protozoa (nonselective disinfectant)

* As of 2019, approved in the US for *Flavobacterium branchiophilum, Flavobacterium columnare,* oomycetes, gyrodactylids in a variety of freshwater-reared finfish and eggs; 0-day withdrawal
  + Degraded to water and oxygen so no residue concerns
* Lower doses used for columnaris and protozoal ectoparasites, higher doses for egg treatments
  + Certain strains of sealice have recently developed resistance
* Toxicity: mortalities in certain species at routine doses, fry more sensitive than adults
  + Increase with increasing water temp
  + Dyspnea, tachypnea, acute mortality

Malachite Green - triarylmethane dye, synergistic with formalin for oomycetes and ectoparasitic protozoa

* \*Carcinogenic and genotoxic
* Use is prohibited in food animal species in the US, EU, UK, and Canada; under high regulatory priority by the FDA
* Use in pet fish should be discouraged

Potassium permanganate - strong oxidizing agent: external bacteria, fungi, protozoa, and monogeneans in freshwater and brackish-water fish

* Immersion: dose based on demand which is affected by organic load
  + Effective dose should maintain a faint pink color in the system for >8hr
  + Brown water: dose too low, dark purple: dose too high
  + To reduce risk of toxicity, wait at least 4 days before redosing
  + Does not usually affect biologic filtration
* At home assay with system water at increasing doses (2-8mg/L) - therapeutic dose is lowest dose that maintains a faint pink color for 15 min
  + If >8mg/L is indicated by the bioassay, organic material should be removed and assay repeated
  + More accurate assay using ORP (redox potential)
* Contraindicated in marine fish
* Adverse effects: lethargy, erratic swimming, dyspnea, tachypnea, dysbiosis, mortality
* Toxic to algae- may deplete oxygen, \*supplementation of aeration or O2 is mandatory during treatment
* NEVER use with formalin - could result in fire or explosion.
* Wear PPE (strong oxidizer)

Fenbendazole - benzimidazole: nematodes, some effect against monogeneans, flagellates, and microsporidia

* Bioencapsulation as been described
* Elasmos and temperate demersal freshwater species reportedly susceptible to fenben toxicity at routine doses (all fish may be susceptible, esp with gavage dosing)
* Tox: neurologic signs, acute mortalities, rays have had digestive and epigonal organ lesions on histo, elasmos have had leukopenia and anemia
  + Most adverse effects occurred after 4-6 days of treatment
  + Use with caution, bioassays essential prior to dosing groups of fish

Metronidazole - bactericidal nitroimidazole: protozoa, some bacteria esp anaerobes, GI flagellates, ectoparasitic protozoa

* Can bioencapsulate
* Anecdotal cases of neuro signs and death, esp pipefish
* Appears relatively safe for inverts

Emamectin - avermectin (lactone macrocyclic antibiotic): crustaceans, nematodes, potentially monogeneans, insecticide

* As of 2019, approved in Canada, UK, Norway, Chile for in-feed treatment of fish lice in salmonids
* Likely efficacious for more than a week after end of oral treatment
* Also effective against swim bladder and intracoelomic nematodes
* Toxic to some aquatic inverts, avoid exposure of nontarget inverts.

Chloroquine - aminoquinolone: external parasites (*Cryptocaryon irritans, Amyloodinium ocellatum,* trichodinids, scuticociliates

* Immersion common, damaged by UV exposure, often persist in water
* High doses or rapid increases can damage biological filtration
* Caution using ozone to remove chloroquine as unknown and potentially toxic by-products may be produced
* Toxic effects on echinoderms and corals anecdotally, may be safe in other inverts (shrimp and crabs)

Levamisole - synthetic imidazothiazole: nematodes, also an immune stimulant

* Toxicity at higher doses
* Can improve specific and nonspecific immune response in fish, used as a vaccine adjuvant
* Residue concerns prevent licensed use - can cause leukopenia and vasculitis in humans
* Dose-dependent inhibition of biological filtration noted with immersions

Niclosamide - salicylanilide derivative: protozoa, nematodes, snails, lampreys esp *Tetrahymena* spp in vitro

* Considered a pesticide, regulated by the EPA in the US
* Low safety index in fish, juvenile lake sturgeons particularly sensitive
* Photosensitive, minimize light during immersion

Phytotherapy: properties obtained from plants

* Oral crushed garlic and immersion with garlic oil can reduce monogenean load in guppies
* Tea tree oil immersion reduced *Gyrodactylus* load in 3-spined stickleback

Praziquantel - quinolone anthelminthic: monogeneans, digenes, cestodes

* Most effective on adults and larvae, eggs and cysts rarely affected, repeat treatments based on prepatent period for egg-laying parasites
* Higher doses more consistently effective but have poor palatability and can cause regurg
* Poorly soluble in water for immersion treatment, manual dissolution through mesh is effect but does not result in full dissolution
* Degraded by bacteria in the system, degrades faster in salt water and with repeated treatments
* No effect on biological filter

Salinity Changes - esp for some ectoparasitic protozoa and monogeneans

* Increased salinity in freshwater for oomycetes, carp edema virus, nitrite toxicity, and to reduce osmotic stress
* Dips: fish commonly show tachypnea, lethargy, recumbency but recover immediately, some fish more sensitive
  + 10 g/L was the mean lethal concentration in zebrafish
  + CS: lethargy, dyspnea, tachypnea, inappetance, mortalities
* Gradual changes in salinity do not usually affect biological filtration
* Avoid salts containing caking agents (sodium ferrocyanide) as they can be highly toxic to fish

Toltrazuril - triazine: coccidia

Trichlorfon or Metrifonate - organophosphate: branchiurans, copepods, monogeneans

* Immersion
* AVOID human contact, toxic and can be absorbed transdermally
* Regulated by the EPA in the US
* Low safety margin esp elasmobranchs: leukopenia, anemia, sudden death
  + Can give atropine prior to treatment to mitigate toxicity from cholinesterase inhibition
  + Concomitant administration of immune stimulant propolis has been shown to mitigate adverse effects in koi

Antifungals: copper sulfate, formalin, hydrogen peroxide, albendazole, salinity changes

* Reports of triazoles are limited to systemic fungal disease in ornamental fish with poor prognosis but seems relatively safe
* Fumagillin - potential option for microsporidiosis but severe adverse effects are common
  + \*Reversible thrombocytopenia in human
  + Alternatives for microsporidiosis: benzimidazoles, toltrazuril, monensin; variable success

Anti-inflammatories

NSAIDS - positive effects reported

* Degenerative and necrotic renal and branchial lesions with diclofenac in rainbow trout
* Perforation of proximal intestine with severe coelomitis and mortality with indomethacin in trout
* Ibuprofen and diclofenac can act as endocrine disruptors in fish

Steroids - use in fish is extrapolated from mammals: adjunctive treatment of shock, trauma, inflammation, and palliative treatment of tumors

* Dexamethasone shown to cause dose-dependent immune suppression in fish as low as 0.03 mcg/kg ICe
* Prednisolone induced immune suppression at 1.4 mg/kg ICe
* Immersion in dexamethasone slowed wound healing at 20 mg/L and led to osteopenia at 1 g/L

Hormones

hCG - used to induce spawning in male and female bony fish

* As of 2019, approved in the US for finfish; 0-day withdrawal

GnRH - used to induce ovulation in bony fish, synthetic analog of salmon GnRH commonly used

* Efficacy varies across species, some studies have mortality up to 35%

Progestins - contraception and treatment of certain reproductive disorders

* MPA used in stingrays to treat polycystic ovaries in all-female groups
* MPA had no contraceptive effect on southern stingrays
* ICe was associated with immunosuppression in common carp

Vaccines

* Oral vaccines typically show low efficacy in fish
* As of 2019, licensed vaccines in the US are commercially available for salmonids against: infectious salmon anemia, infectious pancreatic necrosis, *Aeromonas salmonicida, Vibrio anguillarum, Vibrio ordalii, Aliivibrio salmonicida, Edwardsiella ictaluri, Yersinia ruckeri, Flavobacterium columnare, Renibacterium salmoninarum*
* ISA and IPN usually killed, the rest are MLV
* MLV cyprinid herpesvirus 3 was briefly licensed for koi in the US but adverse effects noted in certain facilities led to removal from the US market
* Autogenous vaccines can be used for specific pathogens/strains isolated in a specific facility
  + The oversight of a veterinarian or other qualified fish health specialist is required and the vaccine must be produced by a USDA-licensed vaccine production facility
  + Oil-based adjuvants typically result in greater antibody titers and longer protection but may be associated with more injection site reactions
  + Should be kept refrigerated and used in less than 1-2 weeks
* Immune stimulants may be given for 2 weeks before and after vaccination to improve success
* Vaccines most effective when given prior to exposure or clinical signs

Immune Stimulants - may reduce or avoid the need for chemotherapeutics

* Little to no effect against intracellular organisms (viruses, *Mycobacterium* spp.) and large parasites (nematodes, copepods)

Beta-glucans - nondigestible glucose polysaccharides found within cell walls of bacteria, plants, and fungi

* B-1,3-glucans and B-1,6-glucans used extensively in aquaculture
* Longer courses (>4wks) typically show no additional benefits
* Higher doses can lead to immune suppression and reduce survival compared to lower doses
* Main indication: short courses at suitable doses prior to a stressor or during an unavoidable stressor

Garlic (Allicin) - crushed garlic contains allicin and other sulfur-allyl compounds with immune-stimulant, antioxidant, hypolipidemic, antimicrobial, and antihypertensive properties

* \*Whole garlic is not effective
* Higher doses and longer courses should be avoided as oxidative tissue damage and acute mortalities have been reported

Propolis - produced by honeybees using plant resins and beeswax

Vitamin C - ascorbic acid, essential vitamin in teleosts

* Elasmos, sturgeon, gar, lungfish, and jawless fish seem able to synthesize some vitamin C
* Requirements are higher in juvenile fish and may increase 3-10-fold under stress
* Heat labile, light-sensitive - stabilized oral forms should be used and stored/prepared appropriately
* No adverse effects, no ceiling effect
* Requirement for vitamin C is affected by level of vitamin E in the diet

Clinical Guide to Fish Medicine (Hadfield/Clayton) Chapter A12 Medical Treatment, Legislation pg. 252-255

Legislation

International legislation

* Some regulations apply to fish such as CITES, international air transport association’s live animal guidelines, and OIE regulations
* However, fish medical treatments are not regulated internationally, great variability between countries

Legislation in the US

* Drugs regulated by the FDA
  + Withdrawal times must be included on the drug label
  + Only a few drugs are FDA-approved for use in aquaculture. As of 2019, these are florfenicol (Aquaflor), sulfadimethoxine–ormetoprim (Romet-30 and Romet-TC), sulfamerazine (no longer on the US market), oxytetracycline dihydrate (Terramycin 200 for Fish), oxytetracycline hydrochloride (for vertebral marking; various trade names), hydrogen peroxide (35% Perox-aid), formalin (various trade names), chorionic gonadotropin (Chorulon), chloramine-T (Halamid Aqua), and tricaine methanesulfonate (Tricaine-S®).
  + Off label use of drugs is permitted under certain circumstances (valid VCPR, adequate withdrawal ensured, must be used o treat a disease where morbidity or mortality would result from lack of treatment)
    - Not allowed to put ELDU in feed
  + Some drugs are prohibited in food-fish in the US. Prohibited drugs include chloramphenicol, fluoroquinolones, vancomycin, dimetridazole, metronidazole, nitrofurans, malachite green, and steroid hormones
  + Some drugs are low priority, ie not officially approved but FDA is unlikely to object (ie sodium chloride, povidone iodine etc)
  + A drug may also be administered under the Investigational New Animal Drug regulations if being used for clinical investigation
  + Compounding is currently allowed when the source is an FDA-approved drug provided the conditions for extra-label use are met
* Vaccines regulated by APHIS
* Pesticides regulated by the EPA
* Water discharge may also be regulated by a local National Pollutant Discharge Elimination System (NPDES) in the state in which the drug use is occurring.
* State or local legislation may be more stringent than national legislation

Legislation in Europe

* legislation regarding fish treatments is made by the European Commission and translated into legislation in each member state (country), which can be more restrictive.
* Salmonidae are considered major food-producing species while other species are considered minor food-producing species
* In some EU states, several ornamental fish species are considered domestic animals
* Currently approved drugs include bronopol, diflubenzuron, emamectin, florfenicol, flumequine (a first-generation fluoroquinolone), gentamicin, oxolinic acid, oxytetracycline, and trimethoprim–sulfadiazine.
* Withdrawal times are based on the maximal residue levels (MRLs) defined by the European Food Safety Authority (EFSA).
* Prohibited drugs for foodstuff of animal origin are listed in Annex IV of the European regulations and include chloramphenicol, chlorpromazine, colchicine, dimetridazole, metronidazole, nitrofurans, and ronidazole
* Some EU countries further prohibit the use of certain antibiotics in all animal species, which may include vancomycin, certain fluoroquinolones, third- and fourth-generation cephalosporins such as ceftazidime, and antibiotics used against mycobacteriosis.
* Some antibiotics can only be used if a bactereial culture has determined they are the only appropriate treaetment

Pathology of Wildlife and Zoo Animals (Terio, 2018) Chapter 39 Osteichthyes, Infectious Diseases, Viruses pg. 962-970

* Infectious diseases
  + DNA viruses
    - Lymphocystis
      * Cultured and wild, FW and SW
      * Lymphocystis disease virus LDV (iridovirus)
      * Icosahedral, diameter 200 nm
      * LDV-1
        + Flounder and place
      * LDV-2
        + Dab
      * Iridoviruses isolated from other species have not been formally characterized.
      * Incubation period – long, weeks to months.
      * Clinical history related to stress.
      * Transmission – horizontal, abrasions of lesions and release of iridovirus into environment.
      * Self limiting.
      * Gross lesions – variably sized, raised, white to tan masses, skin MM, gills.
      * Pinpoint, discrete and nodular, or coalescent and multinodular.
      * Microscopically – extreme cytomegaly of dermal fibroblasts, dermal infiltration by lymphocytes and histiocytes.
      * Dx – microscopic examination of histologic sections or wet mount, cytomegalic dermal fibroblasts.
    - Systemic iridoviruses
      * Genera Megalocytivirus and Ranavirus
        + FW and marine, global distribution
      * Megalocytoviruses
        + Pathogens of fish
        + RSIV – Red sea bream iridovirus
        + ISKNV – Infectious spleen and kidney necrosis virus

These two are the best known, OIE listed.

* + - * + BCCIV – Banggai cardinalfish iridovirus

The only megalocytivirus reported in marine ornamental fish.

* + - * + CS – lethargy, anemia.
        + Gross lesions – branchial hemorrhages, splenomegaly.
        + Histo – cytomegalic cells in multiple organs.

Granular basophilic viral inclusions that distend the cytoplasm and are often located beneath the endothelium of blood vessels.

* + - * Ranaviruses
        + Fish and other spp
        + EHNV – Epizootic haematopoietic necrosis virus
        + ECV – European catfish virus.
        + SGIV – Singapore grouper iridovirus
        + Frog virus 3
        + Influenced by stressors i.e. temp, transport, crowding, mating behavior, malnutrition.
        + Systemic, necrotizing disease.

i.e. EHNV – multifocal necrosis of renal hematopoietic interstitium, liver, and spleen.

Foci of necrosis often centered on blood vessels.

Round, eosinophilic intracytoplasmic viral inclusions.

* + - * Iridoviruses are very stable in the aquatic environment.
      * Transmission – horizontal by ingestion of infected tissues, contaminated water.
      * Dx – virus isolation, IF staining of tissue imprints and cytology, PCR.
        + Spleen, liver, kidney.
    - **Herpesviruses**
      * Three alloherpesviruses affect carp, koi, and/or goldfish
      * Cyprinid herpesvirus 1 (CyHV1; carp pox)
        + Carp and koi
        + Usually self-limiting, primarily a cosmetic problem.
        + Adult fish

Soft, friable, translucent pink, papillomatous or plaque like areas of epidermal hyperplasia.

Mortality in fish fry with exophthalmos and hemorrhage.

* + - * Cyprinid herpesvirus 2 (CyHV2; goldfish herpesvirus, herpesviral hematopoietic necrosis virus)
        + Juvenile goldfish
        + Can cause high mortality.
        + Target is hematopoietic tissue of head kidney, necrosis can lead to profound anemia, infarcts in gills.
        + Large, amphophilic, Cowdry Type A, intranuclear inclusions numerus.
        + Elevating water temp can be key to prevent and control CyHV 1 and 2.

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* Cyprinid herpesvirus 3 (CyHV3; koi herpesvirus)
  + Koi and carp industries
  + Gills are primary target.
  + Severe, segmental, necrotizing and proliferative bronchitis, high mortality for all ages.
* CyHV1 and CyHV2 have worldwide distributions.
  + CyHV2 has been associated with significant losses in farmed populations, prevent with husbandry.
* CyHV3 outbreaks usually caused by introduction of the virus into naïve populations, OIE listed.
  + High mortality, sporadic outbreaks continue.
* Dx immunologic assays, Ab persist for years following initial infection.
  + Amount of active virus in carriers usually negligible, cell culture and PCR not reliable unless active dz causing infections.
* RNA viruses
  + Infectious pancreatic necrosis (IPN)
    - Highly contagious, young salmonids, worldwide.
    - Bisegmented, ds RNA, Birnaviridae family
    - Most commonly rainbow trout, brook trout, brown trout, atl salmon, pacific salmon.
    - Halibut, flounder, cod, yellowtail, turbot.
    - Many others asymptomatic carriers.
    - Species susceptibility reported to decrease with age, correlate with population rearing intensity, temperature, transfer from FW to SW.
    - In FW – corkscrew or spiral swimming behavior, dyspnea, severe abdominal swelling, pigmentary darkening of the body.
      * Post-transfer to SW – anorexia, lethargy, abnormal swimming patterns, unable to maintain buoyancy.
      * Darkening of skin along tail and abdomen, pale yellow liver, GI tract containing pale yellow catarrhal exudate.
    - Histo – severe pancreatic acinar cell necrosis, epithelial necrosis of intestinal mucosa.
      * Pancreatic tissue replaced by fibrous connective tissue.
      * Cytoplasmic viral-specific tubules and paracrystaline arrays of virions on TEM.
    - Sampling – Virus isolation (liver, spleen, kidney, brain, ovarian fluid during spawning.
    - Can be isolated from asymptomatic fish that may be reservoirs.
    - Economic impact of IPN:
      * Millions of dollars, concern for impact on wild populations.
  + **Infectious salmon anemia virus (ISAV)**
    - Causes infectious salmon anemia (ISA)
    - Marine, farm-raised atlantic salmon.
    - Initially described in Norway, since identified in farmed salmon in FW and SW.
    - Isavirus genus (only spp), only fish orthomyxovirus described to date.
    - Enveloped, 8 ssRNA segments, negative polarity.
    - Demonstrated to agglutinate erythrocytes from a range of different fish species.
    - Virulence associated with highly-polymorphic region (HPR) or the hemagglutinin-esterase (HE) gene, and there is a marked difference in virulence of geographically different strains.
    - Sea-run brown trout, rainbow trout, and Coho salmon subclinical disease, reservoirs.
    - High mortality in experimentally infected rainbow trout.
    - Transmission horizontal, carried in SQ contaminated with urine or feces.
    - Sea lice implicated as a vector.
    - Seasonality appears to play a role.
    - Primary mortality between 6-10 months following the intro of naïve salmon to salt water pens.
      * Acutely infected animals typically display evidence of abnormal swimming behavior and marked lethargy.
      * Necropsy – ascites, exophthalmia, severe pallor of the gills and viscera.
      * Petechiae, ecchymoses, liver and spleen often markedly congested.
      * With chronicity, petechiation extends into the subcutaneous adipose.
      * Necrohemorrhagic hepatitis, renal interstitial hemorrhage, and noninflammatory tubular epithelial degeneration and necrosis.
      * Congestion of branchial filaments, gastric and foregut lamina propria, spleen.
    - Viral antigen can be identified in tissue smears using immunoflorescent antibody tests (IFAT).
    - Effective RT-PCR assays.
      * Mos tsensitive diagnostic test followed by VI and IFAT.
    - Large economic impact.

A picture containing text, fish, shark

Description automatically generatedA sandwich with meat and cheese

Description automatically generated with medium confidence

* Viral hemorrhagic septicemia virus (VHSV)
  + Farmed fish, rainbow trout and turbot.
  + Has since been described in over 50 spp of marine and FW fish.
  + Salmonids (brown and rainbow trout), muskellunge, smallmouth bass, walleye lake whitefish, FW drum, atl herring.
  + Rhabdovirus, Novirhabdovirus genus.
    - Can cross species barriers.
  + Transmission through predation or scavenging of diseased or dead fish, thorugh contamination of water with urine or feces, mechanical human or bird vecros, leeches, prey species i.e. amphipods.
  + Three forms:
    - Acute, chronic, nervous.
    - Acute – sudden death up to 100% fry.
      * Darkening of skin, lethargy, exophthalmia, ascites, abdominal distention.
      * Petechiae at base of fins, gills, mouth, eyes, and multifocally along skin.
      * Branchial pallor, abnormal swimming.
    - Chronic – swimming behavior more lethargic.
    - Nervous – hyperactive, abnormal spiraling patterns, flashing and jumping from the water.
  + Gross lesions – hemorrhage, renal congestion, hepatic pallor.
  + Chronic stage similar changes, mortality is decreased.
  + Endothelium is primary target cell.
    - Lytic parenchymal necrosis in liver, kidney, heart.
    - Vasculitis.
    - Aerocystitis.
    - Bullet shaped virions.
  + Confirmation with immunohistochemistry, VI, RTPCR, IFAT, ELISA.

Soto, E., Tamez-Trevino, E., Yazdi, Z., Stevens, B. N., Yun, S., Martínez-López, B., & Burges, J. (2020). Non-lethal diagnostic methods for koi herpesvirus in koi Cyprinus carpio. *Diseases of aquatic organisms*, *138*, 195-205.

**Abstract**Cyprinid herpesvirus 3, also known as koi herpesvirus (KHV), is a viral pathogen responsible for mass mortalities of carp worldwide. In this study, we **compared the sensitivity and specificity of ELISA and quantitative PCR (qPCR) methods for the diagnosis of KHV in experimentally infected koi Cyprinus carpio over an 11 mo period.** Koi were exposed to KHV at 18 ± 1°C (permissive temperatures for KHV disease) in laboratory-controlled conditions. At 21 d post challenge, the temperature in the system was decreased to <15°C (non-permissive temperature for KHV disease), and fish were monitored for the following 11 mo. At different time points throughout the study, samples of blood and gills were collected from exposed and control koi and subjected to qPCR and ELISA. Survival proportions of 53.3 and 98.8% in exposed and control treatments, respectively, were recorded at the end of the challenge. Traditional receiver-operating characteristic analysis was used to compare the sensitivity of the ELISA and blood and gill qPCR during permissive and non-permissive temperatures. **ELISA was superior to qPCR of gills and whole-blood samples in detecting previous exposure to KHV. Similar results were obtained in a second experiment exposing koi to KHV and inducing persistent infection at >30°C (non- permissive temperature for KHV disease).** Finally, **KHV ELISA specificity was confirmed** using cyprinid herpesvirus 1-exposed koi through a period of 3 mo. This study demonstrates that the combination of **ELISA and gill qPCR should be recommended in the diagnosis of KHV exposure of suspected carrierstate fish.**

Introduction:

* Koi herpesvirus (KHV) is a highly lethal virus of koi and common carp *Cyprinus carpio*
* High mortality as 80−100%, non-specific clinical signs i.e. lethargy, gill discoloration, hemorrhage and necrosis, enophthalmia, skin depigmentation, erosions and ulcers
* Histo - **gill necrosis, hyperplasia and branchitis** most commonly reported
* Family Alloherpesviridae
  + Cyprinid herpesvirus 1 (CyHV-1) - ‘carp pox,’ self-limiting, epithelial hyperplasia
  + Cyprinid herpesvirus 2 (CyHV-2) - herpesviral hematopoietic necrosis, mortality in goldfish *Carassius auratus*
* CyHV-1 can cross react with KHV on KHV- ELISA tests, thereby reducing specificity
* KHV disease (KHVD) **causes clinical signs and mortality in the range of 16−28°C**
* Fish that survive infection with KHV can become persistently infected with the virus **–** virus remains dormant in lymphocytes, recrudesces under periods of stress and permissible temps, asymptomatic carriers are problematic
* KHV is a notifiable disease agent by the World Organization for Animal Health (OIE 2019).
* **The OIE recommends at least 2 different diagnostic methods be used for the diagnosis of KHVD due to low sensitivity of some methods and lack of appropriate validation of others.**
  + Confirmatory methods including viral isolation, serological methods and/or molecular methods are recommended.
  + **The Gilad Taqman real-time PCR assay appears as the most widely and frequently used diagnostic method for KHV infections (OIE 2019).**

Materials and Methods:

* **Challenge 1: Permissible temperatures of 18 ± 1°C for 21 d.**
  + Koi exposed by immersion to KHV isolate from an ornamental fish during an outbreak vs controls.
  + Water temperatures were then lowered to <15°C (gradual decrease between Days 21 and 28). Fish kept at lower temp to have lower numbers of antibodies and render them models for testing sensitivity of the ELISA.
  + Following infection, 10 different animals from the treatment groups and 5 different animals from the control group were sampled on Days 1, 3, 7, 14, 28, 42, 56, 70, 87, 112, 143, 171, 199, 227, 255, 283 and 307.
  + Tested KHV ELISA, qPCR of gill tissue, qPCR of blood.
* **Challenge 2: High temp 18−25°C for 31 d following exposure.** Water temperature was then increased to >30°C (gradual increase between Days 25 and 31) to limit mortality.
  + Surviving animals tested at 10, 30, 60, 90 days post challenge.
* **Challenge 3: Cross reactivity of CyHV-1 with the KHV ELISA tested.**
  + Fish inoculated with CyHV-1 by injection, monitored for 7 mos.
  + ELISA developed that was similar to the usual protocol but well plates coated with CyHV-1 antigen. PCR on gill and blood samples performed at end of study.

Results:

* Challenge 1 - Mortality in the exposed animals started at 18 dpc (days post challenge) with exponential increase until 56 dpc.
  + Infected fish presented classic clinical signs and gross lesions of KHV.
  + Detection of KHV DNA was possible from both gills and blood of sampled fish, but **detection occurred earlier in gill samples (7d vs 14d)**
  + Detection of KHV was also **more sensitive when using gills vs. blood**
* Challenge 2 - Mortality in in KHV-exposed fish started at 27 dpc, reaching 63.6% mortality by 50 dpc. No mortalities were observed between 50 and 90 dpc. 8 surviving fish no clinical signs.
  + Detection of KHV DNA was possible from both gills and blood, but similar to Challenge 1, qPCR analysis of **gills was more sensitive** in the detection of KHV DNA
* Challenge 3 – No clinical signs of carp pox in any group. CyHV-1 DNA was not detected in any of the blood, gill or skin lesion samples collected from exposed or control fish.
  + **Quantification of CyHV1 antibodies using CyHV1 ELISA was significantly greater in exposed animals.**
  + **Quantification of antibodies to KHV using the KHV ELISA was similar in CyHV1 exposed and control animals.**

Discussion:

* qPCR analysis of infected gills detected KHV DNA as early as 7 dpc and by 14, 28, and 42 dpc in almost all. Suggests entire tank population was infected after 14 days. Detection of KHV DNA decreased to <50% by 56 dpc.
* qPCR detection of KHV in blood was less sensitive than detection of KHV DNA in gills.
* The first positive blood qPCR samples were detected 14 dpc but rarely over 30% between 14-112 dpc, undetectable after 112 dpc.
* Using the modified ELISA protocol, ELISA had similar specificity as qPCR with greater sensitivity, particularly after 1 month post exposure when fish were persistently infected at non-permissive temperatures for KHV.
* Due to the complementarity of the different diagnostic methods, the combination of ELISA with qPCR of gills both at permissive and non-permissive temperatures should be used to increase the sensitivity of detection of KHV DNA and exposure to KHV
* **Infected fish maintained at non-permissive water temperature may be clinically healthy, but should always be regarded as KHV-positive, as increasing (>30°C) or decreasing water temperature (<15°C) is not curative but can significantly improve clinical signs associated with KHV infections.**

Clinical Guide to Fish Medicine – Ch. C3 – Viral Diseases

* Cyprinid Herpesviruses:
  + Cyprinid herpesvirus-1 (CyHV-1) – Carp pox (plaques, epithelial hyperplasia), goldfish and koi, primarily cosmetic. > 1 yr old. Self-limiting. Mortality in young fish.
    - Ddx white plaques on skin on koi or capr – Carp pox, lymphocystivirus, epitheliocystis, neoplasia.
  + Cyprinid herpesvirus-2 (CyHV-2) – Aka herpesviral hematopoietic necrosis virus HVHNV, goldfish hematopoietic necrosis virus. Hematopoietic necrosis, high morts, goldfish. < 1 yr old. Lethargy, anorexia, dyspnea, ulcerative dermatitis. Renosplenomegaly, white nodules.
  + Cyprinid herpesvirus-3 (CyHV-3) – Aka KHV – Gill and hematopoietic necrosis, mortality in common carp and koi. Goldfish and grass carp asymptomatic carriers. All ages, esp young. Gill necrosis, dyspnea, lethargy. Enophthalmos. Gill necrosis, hyperplasia, edema, widespread petechiae, renosplenomegaly in young fish.
    - KHV is reportable to some state and national groups and the OIE.
    - Ddx skin erythema/ulcers and gill changes in koi or carp – KHV, spring viremia of carp, carp edema virus, viral hemorrhagic septicemia, motile aeromonad septicemia, and Flavobacterium columnare.
  + Etiology: Alloherpesviridae (all fish viruses).
    - Enveloped, dsDNA, icosahedral capsids.
    - Intranuclear inclusion bodies may be seen in affected tissues for all 3 viruses.
  + Transmission – Horizontal, vertical seems likely.
  + Direct contact or water, survives in water for hours to weeks.
  + Permissive water temps are high (60-80F).
  + Dx – PCR for carp pox (skin swab), KHV (gill swab, spleen or kidney). PCR for HVHNV (spleen, caudal kidney).
    - For carriers, qPCR or nested PCR usually needed to increase sensitivity.
    - ELISA can detect Ab in blood for months to a year but may not reliably detect asymptomatic carriers.
    - Recombinase polymerase amplification and loop mediated isothermal amplification tests to detect asymptomatic carriers are being assessed.
    - VI possible but challenging (caudal kidney, spleen).
  + Husbandry management:
    - Carp pox – Slowly increasing water temp by 10F or > 77F.
    - HVHVN, KHV – Isolate fish, increase DO, slowly decrease water temp by 10 F or to < 59F.
      * Depopulation/disinfection may be considered but carriers make it challenging to ensure new animals are negative.
  + Medical management:
    - Low dose hypersalinity to reduce osmotic stress.
    - Follow legislation regarding medication use and disposal.
  + Prevention:
    - Avoid keeping goldfish, koi, other carp in same system.
    - Purchase carp or koi seronegative for KHV with no history of clinical signs when housed at permissive water temps.
    - Isolated quarantine at permissive water temps (72F), prolonged quarantine of 60-90 days.
    - Avoid handling or transport of carp or koi when water temp is 60-80F.
    - Test for KHV by PCR in carp or koi showing morbidity or mortality.
    - Do not mix survivors with susceptible fish or use as broodstock.
    - House fish from different sources in independent water systems and quarantine fish on return.
* Ictalurid Herpesviruses:
  + IcHV-1 – Channel catfish virus CCV; hemorrhagic septicemia in fry or fingerling channel catfish in aquaculture during warm weather. Alabama, Arkansas, Mississippi, Louisiana, California. Central America, Russia.
    - Affects channel catfish (most severe), blue catfish, and hybrids. Fry/fingerlings.
  + IcHV-2 – Similar disease in black bullhead catfish in aquaculture, not in NA, high risk if introduced. Italy.
    - Only black bullhead catfish.
  + Etiology – Alloherpesviridae. Enveloped, dsDNA virus.
  + Horizontal and vertical transmission. Lifelong carriers.
  + Virus does not survive in environment i.e. 2 days at 77F and 28 d at 40 F.
  + Risk factors:
    - Permissive water temp high (77-82F). IcHV-2 has a wider temp tolerance.
    - Recent introduction of new catfish.
  + Clinical signs (both): Inappetence, abnormal swimming with head-up or erratic spirals, coelomic distension, gill petechiae or pallor, exophthalmia, hemorrhages on fins and ventrum.
  + Morbidity and mortality is typically low but can reach 100% with other stressors.
  + Ddx – CCV, Edwardsiella ictaluri, motile aeromonad septicemia, Yersinia ruckeri.
  + Dx – VI (kidney from fresh dead fish with clinical signs). Histology (multifocal necrosis, intranuclear inclusions). SN, FA, ELISA, PCR.
  + Husbandry management:
    - Isolate affected fish. Slowly reduce water temp by 10F to below 66F.
    - Depopulation can be considered but viruses are widespread.
  + Medical management:
    - Control coinfections (abx for E. ictaluri or Flavobacterium columnare).
  + Prevention:
    - Avoid handling or transport of channel catfish when water temp is > 68F.
    - Bullhead catfish, European catfish, and African and Asian catfish may be considered for culture in IcHV-1 endemic areas.
* Rhabdoviruses – Enveloped, RNA virus, classic bullet shape. VHSV, IHNV, SVCV REPORTABLE OIE.
  + Viral hemorrhagic septicemia viruses – VHSV.
    - Aka Egtved disease viruses.
    - 4 genotypes based on geography.
      * VHSV-1 – European FW isolates, particularly of cultured rainbow trout.
      * VHSV-II – Marine isolates, Baltic Sea.
      * VHSV-III – Marine isolates, North Atl Ocean.
      * VHSV-Iva – North Pacific, Japanese, Korean marine isolates.
      * VHSV-IVb – North American FW isolates, Great Lakes region and St Lawrence River, shows a wide host range.
    - RBT particularly susceptible, but all salmonids, FW, brackish, saltwater teleosts.
    - Permissive water temp with highest mortalities 37-54F. No CS > 72F.
  + Infectious hematopoietic necrosis viruses – IHNV.
    - NOT to be confused with epizootic hematopoietic necrosis virus EHNV (ranavirus).
    - Salmonids, west coast of NA, mainland Eu and Asia.
    - Cold FW and SW salmonids. Oncorhynchus and Salmo spp particularly susceptible, especially RBT.
    - Causes disease at 46-59F.
  + Both cause hemorrhagic septicemia in salmonids and other teleosts.
  + Spring viremia of carp virus – SVCV.
    - Hemorrhagic septicemia in cyprinids/koi.
    - Europe and Asia, Brazil, US, Canada. Temperate regions.
    - Koi and common carp, goldfish, crucian carp, minnows, zebrafish, tench particularly susceptible.
    - Causes disease at 52-65F, no CS > 70F.
  + Etiology: Rhabdoviridae, genus Novirhabdovirus and Sprivivirus.
  + Transmission – Highly contagious, horizontal transmission (most), vertical possible (rare).
    - Can persist for days to weeks in water or sediment, or months, survives freezing.
    - Fomites implicated in spread.
    - Fish that recover generally resistant to disease but some become carriers.
  + CS (all) – Nonspecific, lethargy, sporadic hyperexcitability, circling, petechiae, hyphema, coelomic distension, cloacal prolapse, exophthalmos, secondary bacterial ifnections.
    - Mortality varies, can reach 100% in young or naïve fish.
  + Dx – Hemorrhagic septicemia with hematopoietic necrosis.
    - Serosanguinous ascites, visceral pallor, hemorrhages in the swim bladder in cyprinids almost pathognomonic for SVCV.
    - Intranuclear or intracytoplasmic inclusions may be seen.
    - IHNV commonly associated with pancreatic necrosis and inclusions.
    - ELISA, PNT to ID seropositive fish that have been exposed.
    - TEM classic bullet shape.
    - Sample fresh spleen, cranial kidney, heart, and brain for VI and FA, ELISA, or RT-PCR (OIE recommendation).
    - Rhabdoviruses usually easy to isolate and culture.
  + Husbandry management:
    - Depopulation and disinfection. Most countries.
    - US – recommendations provided by USDA.
  + Prevention:
    - Consider surveying female broodstock through ELISAs or VI on ovaries and disinfection of eggs using iodophors.