Fish Health News You Can Use

Brought to you by the Pacific Region Fish Health Program

July 2022 edition

This Issue (#12)

- **Page 1:** Introduction
- **Page 2**: How to Make Treatment Decisions
- **Page 2**: Important Treatment Questions
- **Page 10**: Treatment Example Conundrum
- **Page 14**: What Would You Do?
- **Page 14:** The Rest of The Story
- **Page 15** Treatment Quiz

Contact Us

Pacific Region Fish Health Program Manager
Andrew Goodwin
US Fish and Wildlife Service, Pacific Region 911 N.E. 11th Avenue
Portland, OR 97232
Phone: (503) 231-6784
Email: andrew_goodwin@fws.gov
Website:
fws.gov/office/pacific-region-fish-health-program

In the Next Issue

- The family of Aeromonas bacteria
- Fish health during marking and tagging
- The new FWS Fish Health Policy
- Exotic pathogen? What happens next.

Figure 1: A really exotic parasite. The jellyfish Polypodium from a sturgeon ovary.

Introduction

In the last issue of the Fish Health News (#11), we looked at how fish health problems are diagnosed. There were references to Sherlock Holmes, and fish disease diagnosis was described as a very complicated combination of investigations, interviews, re-creations, and the interpretation of lab results. In this new issue of the Fish Health News, we will take that foundation of diagnosis (how we figure out what is wrong) and use it to address an equally complicated question "How do we decide what to do about it?"

With diseases that are not infectious, the obvious response is to figure out the conditions that are causing the problem and to do our best to fix them. This seems straightforward but, since resources are always limited, it can involve complicated trade-offs. For example, if we clean raceways more often there will be lower ammonia levels and fewer pathogens in the water, but this may also increase fish stress, lead to mechanical injuries, and take hatchery staff away from other duties that may be equally important to protect fish health. Figuring out how to best use the resources available to protect fish welfare, and to maximize fish performance when they are released into the wild, is a difficult balancing act that takes a close partnership between fish health and hatchery managers.

Things can get even more complicated when fish health problems involve infectious diseases. It isn't as simple as saying "The fish have bacterial coldwater disease, antibiotics kill coldwater disease bacteria, we'll treat with antibiotics." Instead, we must recognize that most fish health problems are the result complex interactions between environmental conditions, fish immunity, and infectious disease organisms. In addition, a treatment that works in one time and place may fail at another hatchery or in another season because of minor differences in hosts, pathogens, or the environment. An effective treatment strategy must address not just the disease organisms, but also the underlying environmental conditions that led to the disease outbreak and all of the conditions that impact treatment success.

How to Make a Treatment Decision

In this issue of Fish Health news, we will focus on the complex cases that involve infectious diseases. They are the most difficult because we must deal with interactions between pathogens (organisms that cause disease), the environment, and host susceptibility. The development of an effective response to these disease outbreaks requires that we carefully consider all of the following questions:

1. Why did the fish get this disease?
2. Do we treat the disease, or the cause?
3. Is there a drug treatment?
4. Is the drug treatment legal?
5. Are those treatments safe for people, fish, and the environment?
6. Which of the recognized treatments (if any) is most likely to be safe and effective in this setting?
7. What does the treatment cost?
8. Is the treatment available?
9. Are there regulatory concerns related to treatment storage?
10. Which approach is best for animal welfare?
11. Is this a one-off response to an unusual problem, or something that is likely to be repeated over and over again (sustainability)?
12. Is it time to treat?

Here in issue 12, we will address how we answer all these questions and use the answers to develop treatment recommendations for infectious disease problems on hatcheries. On to question number 1.

The Important Treatment Questions

<u>1. Why did the fish get this disease?</u>

Infectious diseases happen when pathogens (bacteria, viruses, parasites, fungi…) are able to overwhelm host defenses. Any treatment decision must start with looking at why the fish are losing the battle with the pathogen. In a normal situation, the fish and the pathogen are both present, but the fish's defenses are good and the pathogen doesn't do much damage.

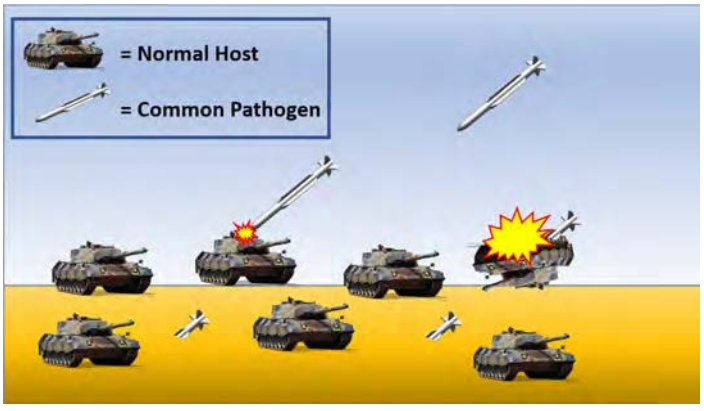


Figure 2: Even when serious disease outbreaks are not underway, there is a continuous battle between fish and their pathogens. If the fish are healthy and pathogen numbers are low, the fish's defenses are strong and they suffer very few losses.

When major fish losses do occur, one reason why the fish might have lost the war against disease is that the fish were overwhelmed by superior numbers of enemy troops (pathogens). Unusually high numbers of pathogens can happen when water supplies contain infected fish, when pathogens propagate in biofilms, when flows are low, in re-use systems, or when pathogens are passed down from infected adults through eggs. If these conditions exist, a treatment (and future prevention) is unlikely to be successful until the number of pathogens is reduced.

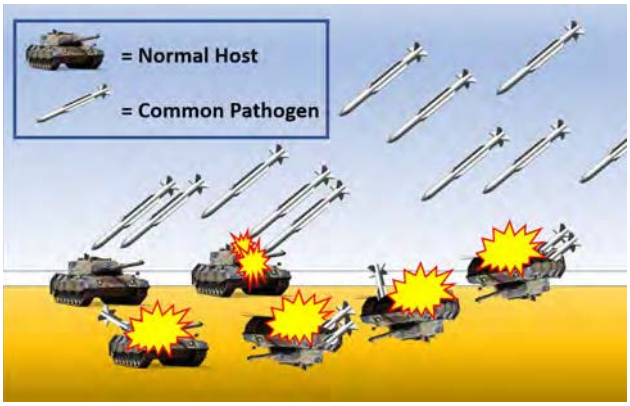


Figure 3: If the numbers of pathogens are high, they can overcome even good defenses.

A second situation associated with major disease losses occurs when the fish are attacked by an enemy that they have never seen before. Surprise attacks happen when new pathogens are introduced through water, fish and other animal movements, or equipment. Efforts to prevent future outbreaks must include steps to prevent the introduction, or reintroduction, of dangerous exotic pathogens.

Some of the biggest fish kills ever seen in the wild have been caused by the introduction of a new pathogen into a fish population that has never seen it before. One recent example is the introduction of the VHS virus into the Great Lakes. Large fish kills occurred for several years until the fish populations adapted its defenses to deal with this new disease.

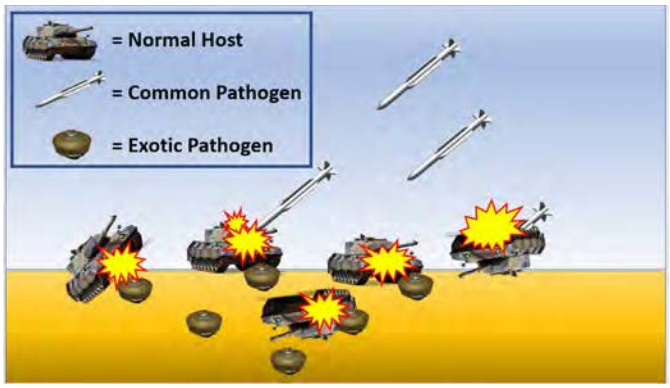


Figure 4: The tanks are well defended against their usual foes (missiles) but in the army's first encounter with a new weapon (mines), weak armor on their undersides may leave them vulnerable.

The third situation that leads to major disease problems is when the fish are losing the disease war because of weak defenses.

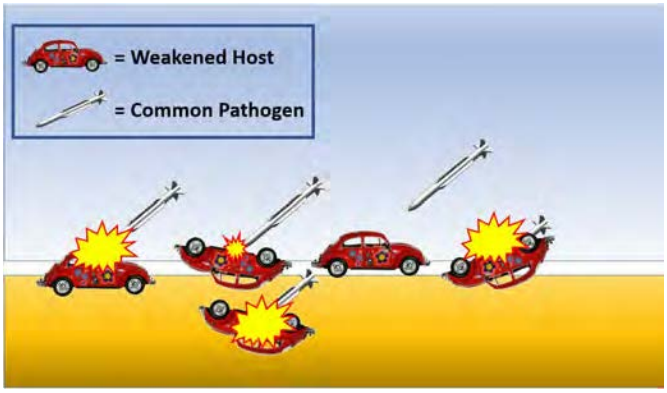


Figure 5: If the host is weak, even common pathogens in low numbers can result in heavy losses.

There is a long list of things that can weaken a fish's immune system:

- Environmental stressors- pH, oxygen, dissolved gas pressure, temp, organic load, turbidity, crowding, social interactions, photoperiod, predators, over-exercise, things perceived as predators
- Exposure to toxins and toxicants - carbon dioxide, ammonia, algal toxins, metals, chemicals, disease treatments
- Early development problems - egg quality, adult nutrition, spawning

operations, and incubation conditions (temperature, turbidity, turbulence)

- Other infectious diseases –bacterial, viral, fungal, or parasite loads predisposing the fish to this disease
- Physical damage to skin and kills – handling, cleaning, biting, predators, sharp/rough surfaces
- Nutrition – incorrect energy or nutrients, feed quality (bad lipids, toxins), amount, frequency, pellet size
- Genetics – sometimes we see outbreaks that seem to hit just one egg lot

If we don't figure out why the fish have become weakened, and fix it, any drug or chemical treatment approach is almost certain to fail.

2. Do we treat the disease, or the cause?

In some cases, a disease outbreak can be stopped by remedying the problems that caused it to occur (all of the things listed in #1 above). In other situations, the infectious disease has weakened the fish enough that improving environmental conditions, feed quality, water quality, or handling may not be enough to allow the fish to win the disease war. This is when drug treatments may be required. In every case of infectious disease, the fish health expert must decide if treating the disease outbreak by fixing the environmental problem is sufficient, or if drug treatments will be needed.

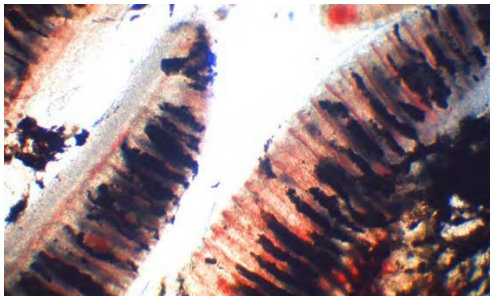


Figure 6: Iron oxide (rust) accumulating on the gills of a fish exposed to water high in dissolved iron. No infectious disease problem could be cured until this environmental problem is fixed.

In some cases, the underlying environmental problem cannot be fixed, for example, a well failure that reduces the water supply. If the environmental problem cannot be fixed, it is very possible that a drug treatment will bring little or no reduction in mortality. Drugs are a great tool, but defeating an infectious disease usually requires that the fish's immune system does its own part to win the war. We can't rely on drugs to make up for serious problems in the environment or fish husbandry.

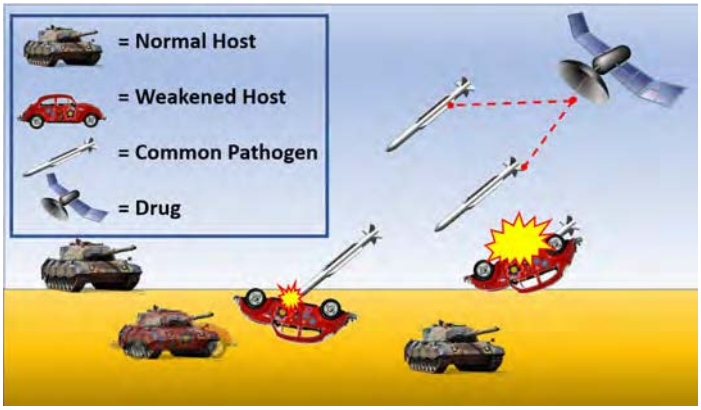


Figure 7: The most effective way to beat the disease war is to strengthen the army, but additional weapons may still be needed to win the war.

3. Is there an effective drug treatment?

There are many important infectious diseases of fish for which there are no known effective treatments. These include some parasites like *C. shasta* and flukes (black spot and salmonicola) as well as viruses and drug- resistant bacteria. In these cases, the only solutions may be to strengthen the fish host, reduce the number of common pathogens entering the system, exclude untreatable pathogens in the first place, or to destroy the fish and disinfect the culture system.

It is also important to keep in mind that sick fish are often off feed so medicated feeds may be ineffective. For a treatment to be effective, the pathogen has got to be susceptible and (for systemic diseases) the drug must get into the fish.

4. Is the drug treatment legal?

Illegal drug use is dangerous to fish, people, the environment, and the reputation of the U.S. Fish and Wildlife Service. It can result in fines, jail time, and the suspension of veterinary licenses. Unfortunately, the regulations governing drug and chemical use in fish are very complex and it is easy to make mistakes. One of the many reasons why our region employs fish veterinarians is that these professionals are experts at understanding drug regulations. In addition, veterinary oversight is increasingly a legal requirement for drug and chemical use in fish.

Figure 8: The AADAP publishes a handy guide for aquaculture drug use.

The most important thing to remember is that drug labels are the law, and that they are governed by the Food and Drug Administration (FDA). For medications used for food-producing fish, including medicated feeds under veterinary feed directives (VFDs), immersion treatments, and injections, the drug labels include information regulating the species for which the treatment can be legally used, the pathogen against which the treatment can be used, the dose, the duration of treatment, and information on whether the treatment can be combined with another treatment concurrently. To make things even more complex, drug labeling is product specific, not active ingredient specific. Parasite-S, for instance, is a formalin product with 37% active ingredient and is labeled for use against external parasites and *Saprolegnia* in fish. Parasite-S would not be legally interchangeable with another 37% formalin-containing product because the label governs the use of Parasite-S and not formalin. Some treatments, like formalin and hydrogen peroxide, can be used without a prescription ***as long as they are used within the strict confines of the label***. Others, like medicated feeds, can only be used under the direction of a licensed veterinarian.

What if the needed use isn't on the label? The FDA does allow for certain medications to be used in an "extra-label" fashion, which means that they are prescribed by a veterinarian to treat a condition that is not on the label, to treat at a different dose, or to treat a species that isn't on the label.

Figure 9:In our region, the two species that we treat with off-label prescriptions most commonly are sturgeon and lamprey. These species are never mentioned on labels.

There are fewer drugs labeled for species that are not common in commercial or conservation aquaculture, so extra-label treatment is often the only option. We extrapolate treatment data from other species to guide our prescription. Part of this extrapolation process includes estimating a withdrawal time (the period of time required for drugs and their residues to be completely metabolized out of the animal). For extra label prescriptions, we often estimate withdrawal times very conservatively and err on the side of a longer withdrawal time to ensure the drug is cleared

from the animal prior to release. Extra-label use of drugs is similar to a VFD in that it requires close cooperation with a veterinarian to ensure that the animals receive a full and effective treatment course, that drug residues are accounted for, and that the treatment is within the FDA's regulatory guidelines.

Rules for extra-label use of medicated feeds are even more restrictive than those for immersion or injection treatments. Extra-label use of VFD drugs in all animals is expressly forbidden, even for veterinarians. However, the FDA recognizes that there are few labelled drugs for some minor species (like lamprey and sturgeon) so the FDA has stated that it is unlikely to take regulatory action against extra-label VFD use in minor species when there is veterinary oversight, a clear diagnosis, a treatment plan, a withdrawal period, and important animal welfare or endangered species concerns. We only undertake this route in careful consultation with the FDA to ensure good antibiotic stewardship, add to the growing body of knowledge about drug use in minor species, and optimize the health and welfare of the animals in our care.

Figure 10: Service Veterinarian Katie Royer performs a surgical procedure on an anaesthetized fish.

In addition to label use and extra-label use under veterinary supervision, there are also several drugs that can be used under an "Investigational New Animal Drug" (INAD) process for specific purposes. The INAD process is overseen by the Service's Aquatic Animal Drug Approval Partnership (AADAP), which seeks to expand drug labels and options for aquatic species. There is a very detailed process for INAD approval and reporting and any INAD use on National Fish Hatcheries in our regions must be coordinated through the PRFHP. In some cases where an INAD is an option, the FDA has still recommended an extra-label prescription to ensure that there would be veterinary oversight and follow up to ensure the fish had cleared the infection.

Drug use rules are complex, and meeting legal requirements is often a significant part of making treatment decisions. The good news for hatchery managers is that the PRFHP staff has the expertise and connections to make sure that any drug and chemical use meets the highest legal standards.

5. Is the potential treatment safe for people, fish, and the environment?

Even when there is a legal and effective drug for a fish disease, there are still difficult questions to be answered.

- Are the fish strong enough to tolerate the treatment?
- What are the risks to humans applying the treatment?
- Will it lead to resistance in other important human and animal pathogens?
- What is the environmental impact of the treatment?

All drugs and chemicals have side effects, and all can be toxic or ineffective in the wrong dose, under the wrong conditions, or through accidental exposure. This is an especially

important consideration in fish health where the amount of drug or chemical needed to treat a large system is far greater than that which would be used to treat terrestrial animals in farm or home settings. Human safety comes first.

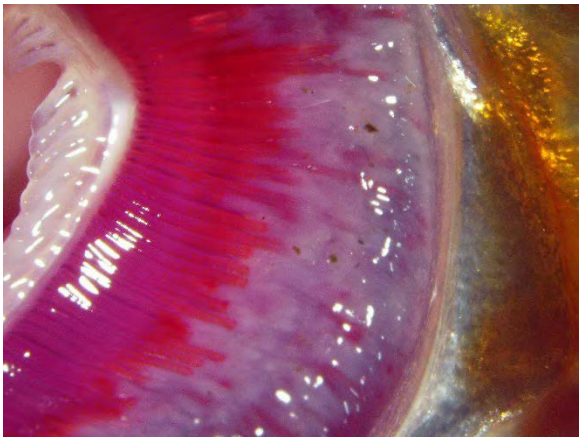


Figure 11: An accidental overdose has damaged this gill. Blood is no longer flowing to the tips of the filaments.

6. Which of the proposed treatments (if any) is most likely to be safe and effective in this setting?

The effectiveness, and risks, of drug and chemical use are highly influenced by many conditions that differ from case to case. These include:

- Water quality- The toxicity and effectiveness of many drugs (chloramine-T for example) is very dependent on water quality especially pH, hardness, and alkalinity. A drug that is safe and effective in one setting may be ineffective or toxic somewhere else.
- Seasons and temperatures – Because of differences in chemistry and metabolism, a drug that is effective at one temperature may be toxic or ineffective at others.
- Host species – Different species metabolize drugs differently. A treatment that is safe and effective in one species may be toxic in another. For example, Diquat is great for columnaris in many species of fish but causes severe liver damage in smallmouth bass.
- Fish size and life stage- Small fish have greater surface area to volume ratios than do large fish. In addition, they eat a higher percentage of their body weight every day, and they metabolize drugs differently than larger fish.
- Impacts on long-term performance – Will the drug treatment have side effects that might compromise the future performance of the fish? Survival to release is great, but adult returns are what really matters.

Figure 12: The chemistry of copper sulfate (used to control parasites in pond aquaculture). When alkalinity is low, copper stays in solution and is very toxic. At high alkalinity it precipitates out as copper carbonate so quickly that parasites are not killed.

7. What does the treatment cost?

The cost of medicated feeds, or of expensive drugs in large systems, can be formidable. It would be great if we could always afford the very best possible treatments, but in the real world there are budgets. The cost/benefit ratio must be taken into consideration.

8. Is the Treatment available?

There are often cases where we have to balance long delays for obtaining the preferred treatments against the immediate availability of a less effective treatment. Is it better to treat with a less effective drug now than it is to wait for the best drug later?

Figure 13: Due to the small size of the market for aquaculture drugs, availability is easily impacted by production problems, import regulations, and supply chain disruptions.

9. Are there regulatory concerns related to storage?

Some drugs, especially strong oxidizers, come with additional regulatory burdens related to safe storage and terrorism risks. That extra regulatory burden must be taken into account.

10. Which approach is best for animal welfare?

It is difficult, if not impossible, to know if fish perceive pain and distress in the same way as humans and higher animals, but our ethical choice is to treat them as if they do. Our treatment goal is to have the same sensitivity toward fish as we do for dogs and cats. Our responsibility is to do everything that we can to reduce the potential of pain and distress. This means dealing with diseases promptly, and with treatments that do not unnecessarily add to the pain and distress burden. In cases where disease is untreatable and progressing, the humane choice may be to euthanize the fish. When euthanasia is used, we follow the strictest guidelines to make sure that it is done humanely.

We must also consider the welfare of other fish and animals that might be affected by interacting with diseased fish. The potential of a disease to spread from fish on a hatchery to fish in the wild is always a concern that we address in making treatment decisions.

11. Is this a one-off response to an unusual problem, or something that is likely to be repeated over and over again (sustainability)?

A single outbreak of a disease is very different than a pattern where the disease is a regular problem. For example, a single outbreak of a bacterial disease that responds well to a labelled antibiotic is no big deal. However, if the disease occurs often, each use of that antibiotic increases the probability that antibiotic resistance will develop. That resistance compromises all future use of that antibiotic on the hatchery, and perhaps on other hatcheries. There is also concern that resistance genes could move from fish pathogens to other human and animal pathogens.

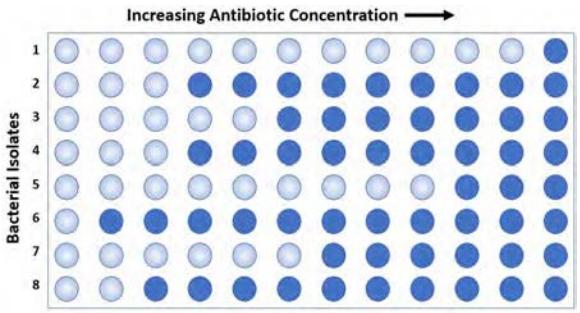


Figure 14: To test for antibiotic resistance, bacteria (light blue) are grown in a series of increasing antibiotic concentrations. On this test plate, Bacteria #1 is the most resistant to the antibiotic and #6 is the most sensitive.

The development of resistance to drugs with broader actions (formalin, peroxide, chloramine-T) is not as big a risk as we face with

antibiotic use, but it is still possible to select for resistance. Many bacteria carry genes that enable them to detoxify peroxide, bleach, and formalin. Development of resistance in more complex eukaryotic or multicellular organisms to broadly acting drugs is much slower to develop, but the potential is certainly there. We have recently heard of an ich strain that has evolved to mature at a smaller size so that it could successfully complete its life cycle by passing through the screen filters in a RAS system.

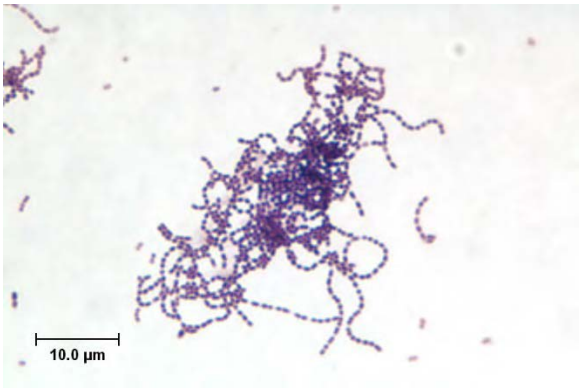


Figure 15: Many species of bacteria make enzymes that break down hydrogen peroxide and bleach because these chemicals are produced and used by white blood cells to kill bacteria. Natural selection at work.

Repeated use of any treatment, especially antibiotics, may not be sustainable. We rotate treatments to reduce the risk, but in some cases repeated use may promote the development of resistance, compromise the effectiveness of future treatments, and increase the risk of antibiotic resistance in humans and other animals. To use drugs in a way that significantly increases these risks is unsafe and unethical.

12. Is it time to treat?

One of the most difficult considerations in treating a disease is to decide if and when to treat. If we treat too late, the disease may be so advanced that no drug will help. On the other hand, if we treat too early, we may cause a lot of fish stress and expense trying to deal with a problem that would never have progressed to a serious disease outbreak. Our goal is to detect diseases early, and then base our treatment decisions on history and on current conditions. If we know that, based on past experience, the disease and conditions that we are seeing are likely to progress to a serious level, we are more likely to treat early. Likewise, if we know that the fish have been stressed by some environmental condition and are now showing signs of infectious disease, we are more likely to treat because we expect that the disease is more likely to become severe. On the other hand, a case with a few sick fish in an otherwise healthy population under good environmental conditions is more likely to result in watchful waiting. We will be on the lookout for increasing severity of the outbreak, and for stressors that might lead to a sudden worsening of the outbreak, but only treat if the situation appears to be worsening.

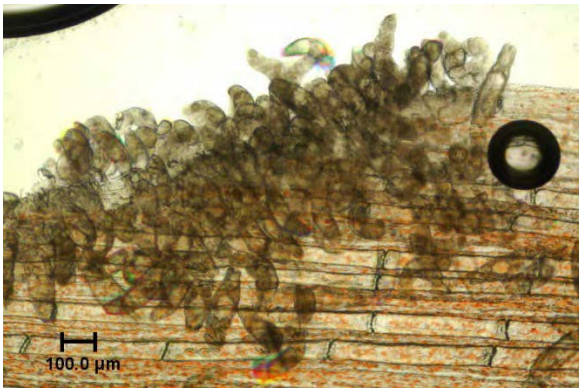


Figure 16: Skin and gill flukes are common on many kinds of fish. They usually exist in low numbers but, under some conditions, populations can explode and severely compromise fish health.

Summary

Treatment decisions are tough. We try to base our decisions on optimizing welfare and on achieving the greatest possible success for the program (usually adult returns). At the same time, we must keep a wary eye on drug regulations, public perception, human health, costs, and the environment. Fundamental to it all is an accurate assessment of the potential

losses if the fish are untreated and an estimate of the benefits of any treatment that might be undertaken. To make the best decision requires expertise in regulations, chemistry, pharmacology, toxicology, microbiology, parasitology, diseases, fish physiology, a detailed knowledge of the health status of the hatchery fish population and the disease history of the facility, and an understanding of the hatchery's facilities and operations.

An Example of a Typical Treatment Conundrum

Infections by bacteria in the "motile aeromonads" group can pose some difficult treatment questions. We'll go through the diagnostic challenges and then look at the treatment questions to plan a course of action.

It is August, a group of Chinook salmon are sick, and samples are sent to the lab. The fish have pale skin, eroded fins, and the internal organs all look unusually red. Mortality is at about 3% per day, up from 1% yesterday and 0.5% the day before. Feed consumption is down by about 50%. From sick fish, the lab cultures a mixture of bacteria that are not recognized fish pathogens, but 3 out of 5 fish also produce quite a few colonies of a bacterium identified as *Aeromonas sobria,* a motile aeromonad.

The first challenges are diagnostic. The motile aeromonas family is huge, diverse, and poorly characterized. Identification by biochemical or DNA sequencing methods often yield ambiguous results and the definitions of species in this group constantly change. For that reason, we usually just refer to the members of this group as "motile aeromonads" and avoid species names that are usually not helpful.

Within the motile aeromonad group are bacteria that are very common as normal flora on fish skin and in their guts. In many cases, it seems like the motile aeromonads fill the same niche in many fish species as E. coli do in humans and their role as "normal flora" may be equally important.

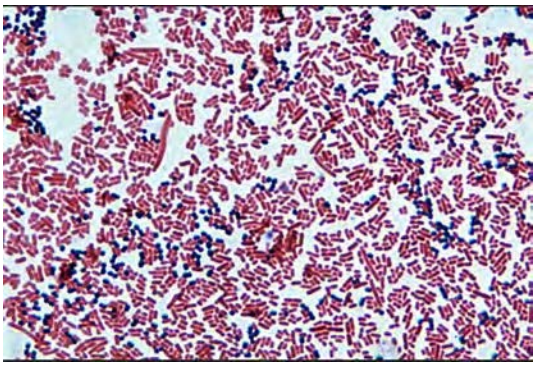


Figure 17: Aeromonas bacteria stained (Gram) and seen under a microscope.

The motile aeromonads are also very common in aquatic habitats. They are found in water, sediments, and on and in other aquatic animals. Unlike some bacteria that must have fish in their life cycles, the motile aeromonads are generally happy to be free living if the need arises.

Among the motile aeromonads, there are species and strains that readily make their way into fish and cause serious infections, and there are others that are rarely a problem. There is no convenient diagnostic test to reveal which strains are adapted to cause fish diseases, and which are not.

Figure 18: A catfish with a motile Aeromonas infection. Pale skin and damaged blood vessels are typical signs.

There are other diagnostic complexities. If all 5 fish submitted for testing had what appeared to be the same disease, why did we only find the aeromonads in 3 out of 5? What does it mean that there were not huge numbers of aeromonads in the cultures where they were found? What does it mean that there was a scattering of other bacteria present in the culture?

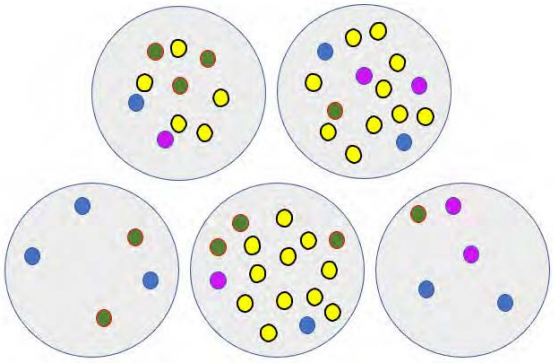


Figure 19: Bacteria cultures from sick fish. Colored spots are colonies of bacteria. Yellow is the recognized pathogen Aeromonas sobria. Other colors are bacteria not associated with disease. What do these cultures tell us?

In general, we consider a culture finding significant if 1) the same bacteria are found in most of the diseased fish, and 2) there are enough colonies of that bacterium on each plate to convince us that it is really causing a disease. We often don't isolate the bacterium from every fish. This is because we may grab an occasional fish that is dying for some other reason, or because we just missed the bacteria when we took the culture (maybe it was in the brain and we cultured the spleen). The other bacteria on the plate are also meaningful. They may be the result of contamination from the gut or skin surface. This is a big problem with very small fish. The other possibility is that an injured or sick fish has become so weak that common environmental bacteria have invaded and we are picking these up in the culture. This is common in diseased fish, and in salmon broodstock as spawning approaches.

In our Chinook salmon case, we know that 1) *Aeromonas sobria* has been reported as a fish pathogen, 2) that we found it in most of the diseased fish, and 3) that the symptoms in the fish are consistent with a motile aeromonad infection. Most fish diagnosticians would conclude that *Aeromonas sobria* was probably an important component in the disease losses. With that decision behind us, we can now look at the treatment questions.

1. Why did the fish get this disease? Given that the motile aeromonads are common in the environment, and on the skin and in the guts of healthy fish, we would usually conclude that these infections are "secondary." By that, we mean that the fish has been weakened by another disease, environmental problem, or injury, and that the bacteria have taken advantage of the situation to switch from being benign to causing a serious infection. When we see these secondary infections, we look very hard for the primary cause. In Pacific salmon, it is usually high temperatures, poor water quality, or skin damage from handling, parasites, or other infections. In this case, it is August and temperatures are high and water flows are low.

Figure 20: High temperatures are a major cause of bacterial infections in salmon. Here, a disease outbreak is treated by moving the fish to a facility with cooler water.

2. Do we treat the disease, or the cause? Because most motile aeromonad infections are secondary, we will always search for another fish stressor and work to control the infection by removing that stress. However, if primary causes are not found (or we cannot mitigate them), and the prevalence and severity of the infection in the fish population is high, drug treatment might be contemplated. In this case, the preferred treatment would be to get the fish to some cool, high-quality water so that the bacteria growth would be slowed and the ability of the fish's immune system to fight off the infection would be enhanced. If that isn't possible, or of the fish seem too sick to move, we'll need to continue to contemplate treatments. In this case, we can't move the fish to cooler water.

3. Is there a drug treatment? There are several antibiotics that might be effective against these motile aeromonads if given in a medicated feed. However, this group of bacteria is famous for having, or rapidly developing, antibiotic resistance. We can do antibiotic sensitivity testing, but is there time before the fish all die? We are already looking at delays while we wait for medicated feeds to arrive. In this case, antibiotic sensitivity data is 3-5 days out.

4. Is the drug treatment legal? There are three antibiotic feeds labeled for fish. Oxytetracycline is labelled for a motile aeromonad (*Aeromonas hydrophila*) in salmonids, but **not** for *Aeromonas sobria*. Romet is labelled for *Aeromonas salmonicida* (which causes furunculosis) but this is not a motile aeromonad and should clearly be regarded as a different bacterial species. Aquafluor is also labeled only for *Aeromonas salmonicida*. Given the ambiguity in motile aeromonad taxonomy, is *A. hydrophila* close enough to justify oxytetracycline use? Since Romet and Aquaflor are labelled for other bacterial diseases in salmonids, can I use them here even though this is a different bacteria species? In this case*, A. sobria* is not on the labels so any treatment requires an extra-label prescription (VFD) from the veterinarian. The best choice, from a regulatory and safety perspective, is to choose the drug that is labeled for a use most similar to the one anticipated. In this case, this means a VFD for oxytetracycline because it is labeled for salmonids and for a very closely related bacterial species (*A. hydrophila*).

5. Are those treatments safe for people, fish, and the environment? If the medicated feeds are used for the labeled fish species and under the same conditions as those described on the label, we can assume that the basic safety requirements have been met. However, there are people with severe sensitivities to some antibiotics. It is also very important to recognize that the motile aeromonads are masters of antibiotic resistance. Even one course of treatment may cause resistant strains to emerge. What's worse, the motile aeromonads are very adept at trading resistance genes with other bacteria, even very different species. There is a good chance that this use will promote antibiotic resistance in in bacteria associated with this treatment.

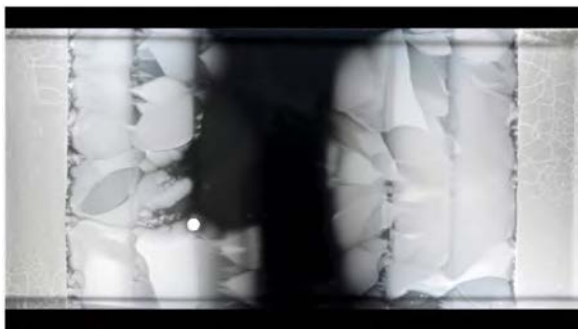


Figure 21: Revisit the awesome U-tube video that shows the evolution of antibiotic resistance (click here).

6. Which of the recognized treatments (if any) is most likely to be effective in this setting? If we have antibiotic sensitivity data, we'll use that data as a big part of our decision. Failing that, we'll look at previous antibiotic use at that hatchery (and try to pick something else), or recognize that oxytetracycline resistance is common in motile aeromonads. Another factor is palatability. Some antibiotics taste bad and, in some circumstances, fish are reluctant to eat the medicated feed. More significantly, if the fish are not still eating well, medicated feed treatment will obviously fail. In this case, feed consumption has dropped by 50%.

7. What does the treatment cost? This depends on the cost of the feed, the amount needed, and on shipping costs (often substantial for rush shipments).

8. Is the treatment available? The availability of these medications is influenced by the season, hatchery location, demand by other hatcheries, and national availability of the antibiotic. The one that we want might be ready for delivery from a nearby mill, or it might be weeks away. In this case, we can get it delivered within 5 days of our order.

9. Are there regulatory concerns related to treatment storage? None with medicated fish feeds. Just keep them cool and dry.

Figure 22: Why are there regulatory and storage concerns about concentrated hydrogen peroxide? Check out this U-tube video. Be sure to wait until the parts with leather gloves and boots (click here).

10. Which approach is best for animal welfare? We have 5 options 1) fix the environmental problems causing the infection, 2) treat the infections with an antibiotic, 3) do both, 4) do neither and just let things run their course, or 5) euthanize the fish. Given the significant mortality option 4 (do nothing) is not very acceptable on animal welfare grounds. Option 5 (euthanasia) would probably not be selected for a disease outbreak caused by a common bacterium when there is just a 2% daily mortality, and we have treatment options. Option 1 (fix the environment) is one that we would work really hard to achieve. Option 2 (antibiotics alone) is probably not going to be sufficient if serious environmental problems exist. From a strictly animal welfare perspective, option 3 (environment and antibiotics) is probably best, but future antibiotic concerns will weigh heavily on any decision to treat. In this case, cool water is unavailable so options 1 and 3 (fix the environment) are not possible. Number 2, treat, is all that is left.

11. Is this a one-off response to an unusual problem, or something that is likely to be repeated over and over again (sustainability)? If these salmon are rarely treated with antibiotics and motile aeromonad infections are an uncommon problem, then antibiotic treatment is a possibility because the risks of treatment leading to antibiotic resistance are minimal. If this is instead a re-occurring

problem, or if we rely on the same antibiotic to treat outbreaks of other diseases on the hatchery (coldwater disease for example), the risks of promoting antibiotic resistance may be too great. In this case, this is our first motile aeromonad outbreak so it is currently a one-off, but the coho on this hatchery often require antibiotic treatment for bacterial coldwater disease with oxytetracycline or Aquaflor (used in rotation to help avoid resistance) so antibiotic use across the facility is already a concern.

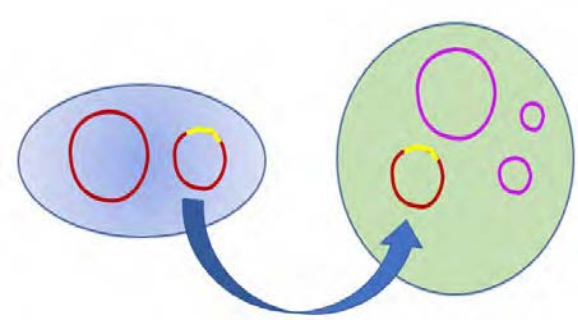


Figure 23: Bacteria love to get together and exchange genes present on small circles of DNA called "plasmids." Here the blue bacterium has just donated a plasmid with a tetracycline resistance gene (yellow) to a different species of bacteria.

12. Is it time to treat? Mortality is increasing, the bacteria are sensitive to an antibiotic, feed consumption is dropping drastically (a sign that a large percentage of the population is sick) and we can't get the fish to cooler water. Things are likely to get worse and treatment seems like a good idea, but with feed consumption way down and the fish still in hot water, are we going to make a real difference in fish health and welfare or just promote antibiotic resistance without making a significant improvement?

So, what would you do?

Is medicated feed a good idea? This is a tough call. Our expectations for effectiveness under these conditions are not high. The decision would be based on a best guess of the future course of the outbreak and on the importance of the fish to recovery or mitigation programs. Antibiotics could be used, but a wait and see approach, followed by euthanasia if losses rise and welfare concerns increase, might be a strong alternative. Ideally, we would focus on getting the fish into some cool clear water, but we ruled that option out in this scenario.

If you did use an antibiotic, which would you choose? Nothing is labeled for this purpose so an extra-label use of a medicated feed with veterinary supervision would be required. This is tricky ground. The first choice would be oxytetracycline because it has a label that covers salmon and a bacterial species very closely related to our *A. sobria* outbreak.

If the results of medicated feed are equivocal (a drop in mortality, but the disease continues to be a problem), would you do it again next time? Probably not. The risk of antibiotic resistance is significant and a potential threat to the hatchery's coho salmon program. Future emphasis needs to be on finding a way to keep these fish cooler, or in changing programs to avoid having fish in warm water.

The Rest of the Treatment Story

The person that makes the treatment decision is also responsible for making sure that treatments are done correctly, that the response of the fish to the treatment is monitored, and that the outcome of the treatment (success, partial success, or failure) is determined and documented.

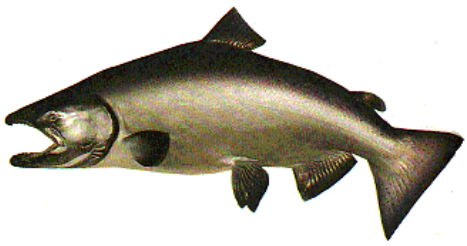
Step 1, Verifying the Treatment: Was the right drug used at the right dose? Step one is to verify that the correct drug, in the specified form/concentration, was used at the specified dose. For medicated feeds, we must look at how much medicated feed was consumed by the fish so that we can calculate the actual drug delivery. For bath treatments, we look at water

chemistry and turnover rates and double check treatment calculations.

Step 2, Fish Response: All drugs have side effects. It is important to monitor the fish during the treatment to look for adverse effects that might require corrective steps (stopping the treatment, flushing bath treatments, reducing dosages). The sicker the fish, the more difficulty they have in tolerating the treatment. Daily mortality data is an important clue, but mortality alone can't differentiate between a failed treatment and a toxic treatment.

Step 3, Follow Up: During and after the treatment, we look closely to see if the drug is having the desired impact on the disease organisms. With parasites, we can often check fish samples under the microscope during and after treatment to see if the parasites are dying. With bacterial infections, we look for a lessoning of symptoms and mortality. Very often, we do follow-up cultures and histology to be sure that the bacteria are gone and that we have not selected for antibiotic resistant strains.

Step 4, Records: It is extremely important that fish health records include not just a diagnosis, but also the treatment strategy undertaken and the success of that treatment. These records are a critical tool to be used in future treatment decisions.



Fish Treatment Quiz

1. Does a formalin treatment for ich require a prescription from a veterinarian?

No, not as long as the treatment is done exactly according to the label. Several brands of formalin are labeled for ich treatment. The label is the law and the label does not require a prescription or veterinary oversight.

2. Is a disease treatment a failure if mortality increases the first day after the treatment?

No. It is not uncommon for fish given bath treatments, with chemicals like formalin or chloramine-T, to experience a spike in mortality after treatment. The spike happens because some very sick fish cannot handle the exposure to the treatment. In general, the fish that die during the spike are fish that would have died anyway had the disease gone untreated. Looking at it another way, the fish that would have died on Monday, Tuesday, and Wednesday if the fish were untreated, might all die on Monday after the treatment. If the treatment is effective, mortality will quickly drop after the spike.

3. Do animal welfare considerations require us to always treat outbreaks of fish diseases?

No. Welfare considerations require us to care for fish as if they experience pain and suffering

in the same way as higher animals. A drug treatment is only appropriate if there is a reasonable likelihood that it will improve the welfare of the fish. Often, efforts to improve husbandry will improve fish health and welfare while the stress of a drug treatment would actually be detrimental. There are also cases where euthanasia is the best option.

4. If fish have serious parasite problems, is it a good idea to treat with antibiotics to prevent secondary infections?

No. Antibiotic use is reserved for situations where fish have a specific bacterial disease, that is sensitive to the antibiotic, and when all of the treatment criteria described in this article are met. It is also important to remember that all drugs have negative side effects. Improper antibiotic use will subject the fish to these side effects without providing any benefit. This may negatively impact health and welfare.

5. When using antibiotic feeds, can we reduce concerns about developing antibiotic resistance if we stop treatment as soon as an improvement is seen?

No. Drug labels require that the treatment be carried out for the full duration specified on the label. Shorter treatment periods may allow partially resistant bacteria to escape and lead to the development of fully resistant strains of bacteria.

6. Should fish disease treatments be started at the first sign of disease?

No. Treatment should only be started when there is a strong expectation that mortality will be significant and when environmental and husbandry improvements are unlikely to be sufficient to stop the disease outbreak.

7. Are medicated feeds the best way to deal with re-occurring bacterial infections?

No. Repeated use of antibiotics leads to the development of resistance and treatment failure. The only effective approach is to change husbandry or programs so that the bacterial infection no longer re-occurs.

8. Do veterinarians have broad powers to use medications in fish as they see fit?

No. Veterinarians are highly constrained by federal and state law. They must follow strict legal mandates or face very significant penalties.

9. Do drug withdrawal times apply to fingerlings that are about to be released into the wild?

Yes. In general, fish cannot be released until post-treatment withdrawal times have passed.

10. If a formalin label calls for a 170 ppm treatment for one hour, is it okay to use a lower dose, or a longer time?

Yes and no. The formalin labels specify "up to 170 ppm" so in this case a lower dose would be legal. It also says "up to 1 hr." This means that a shorter treatment is allowed, but not a longer one. Any departure from the label would require veterinary oversight and a prescription.

11. As long as the label is followed exactly, does medicated feed use always require a prescription (VFD)?

Trick Question! Part of the label is that it requires a veterinary VFD so, to follow the label, a veterinarian must be involved.

The only medicated feed use that does not require a prescription is feed that is used under the Investigational New Animal Drug program (INAD). In this case, the label does not describe the INAD use, but the use is strictly controlled

through a written agreement and reporting structure with AADAP.

12. If you have leftover medicated feed from a veterinarian-prescribed treatment, you can use it to treat other sick fish?

Only with a new VFD from the veterinarian. The prescribed feed must be used exactly according to the VFD under which it was purchased unless the veterinarian is consulted and approves the new use.

13. What about salt? In aquaculture, we use it as a drug, and it doesn't have a fish use label, why is that legal?

Salt is on a special FDA list of "Low Regulatory Priority" drugs (along with ice and even garlic extract). The FDA has stated that it will not prosecute use of these listed "low regulatory priority" drugs as long as they are used in the ways and dosages that the FDA expects.

14. What about potassium permanganate and copper sulfate? There are no fish labels, but they are still widely used.

These two compounds are not formally legal, but they are described by the FDA as "regulation deferred." The FDA has stated that they are not likely to prosecute hatcheries that use these compounds at the usual dosages for the traditional purposes.

15. How do drug withdrawal times affect salmon carcass outplants for nutrient supplementation?

In order for fish to be used for nutrient enhancement, the usual practice is that fish that are injected with antibiotics must go through the complete withdrawal period before they die. This is not possible in fish when drugs, without established withdrawal times, are used.

Figure 24: PRFHP Fish Pathologists Corie Samson (top) and Tim Bundy (bottom). Fish health detectives hard at work!