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Annals of Aquaculture and Research

Review Article

Updated of the Pathologies Affecting Cultured Gilthead Seabream, *Sparus aurata*

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Submitted: 22 March 2017

Accepted: 12 April 2017

Published: 14 April 2017

ISSN: 2379-0881

Keywords

- Gilthead seabream
- Aquaculture
- Pathologies
- Diseases
- Infectious agents
- Skeletal disorders
- Malformational alterations

Abstract

Among other *Sparidae* species, the gilthead seabream *Sparus aurata* is the most important fish species in the Mediterranean aquaculture, achieving good growth performances and progressive increased production. However, health management remains as one of the major concerns of the gilthead seabream culture, because diseases can cause major losses to commercial crops. In suboptimal conditions of intensive rearing systems, the danger of disease outbreaks is always present. Since quarantine restrictions were rarely adopted, several microbial pathogens have been transmitted to other geographic locations, and frequently they have colonized new fish hosts and/or new environments. In this work, we have updated some of the most important and also serious pathologies and diseases that from many years ago and presently affect to reared gilthead seabream specimens, mainly those with uncertain or complex aetiology (genetic, nutritional, zootechnic, among others), such as malformations-vertebral deformities, as well as those more classical and emergent parasitic and infectious pathologies and diseases. In addition, avalaible treatment and/or prophylactic measures are also discussed.

INTRODUCTION

Gilthead seabream (*Sparus aurata*), a member of the family *Sparidae*, is found in the Mediterranean Sea and extends into the Atlantic Ocean from the British Isles south to Senegal. Most countries around the Mediterranean culture gilthead seabream; Greece, Turkey, and Spain are the major producers in the region, accounting for over 70% of total production. The culturing of *S. aurata* has achieved impressive strides in much less than two decades, going from an estimated 110 Tm of fish in 1985 to more than 173,000 Tm in 2013 [1,2]. This success is the result of strong research and development programs in many of the countries, in conjuction with a persistently strong market demand for this fish species. However, the rapid development of gilthead seabream farming has not been paralleled by adequate progress in the veterinary aspects of its culture.

Fish diseases are a primary constraint to the culture of many aquatic species, avoiding both economic and social development in producer countries. This situation can be attributed to a variety of interconnected factors such as, the increased globalization of trade in live aquatic animals and their products; the intensification of aquaculture through the translocation of broodstock, postlarvae, fry and fingerlings; and the development and expansion of the ornamental fish trade to name a few [3]. An adequate aquaculture practice must also consider other matters that are not directly related to fish health because public concerns have a significant influence on how and where fish are cultured. Thus, the environmental impacts of the culture operation, the safety of cutured product for human consumption, and the fish welfare are other important factors taking into account to achieve a sustainable practice of the aquaculture [4].

Most of the diseases that cause serious problems in cultured fish are provoked by exotic pathogens; that is, they were inadvertently introduced into a region via infected fish from another geographic area. Thus, an effective biosecurity programme is vital to maintaining healthy animals and to reduce the risk of adquiring disease in a fish facility. Biosecurity refers to the implementation of methods to prevent the spread of infectious diseases within a farm, and to avoid their transmission to wild fish populations or to adjacent fish farms. Key methods used to maintain biosecurity are pathogen inactivation strategies and avoiding fish-to-fish transmission by mean of geographic isolation of affected farms, separation of diseased fish, specific-pathogen-free stocks, and quarantine measures [5].

In order to minimize the risks of pathogens/diseases associated with aquatic animal movements, there are a number of existing global instruments, agreements, codes of practice and guidelines (International Codes) that, if implemented, provide certain levels of protection. Some of the provisions in the current international protocols are not always practically applicable to the diseases of concern to a specific region. Therefore, a regionally adopted health management programme is considered a practical approach. Subasinghe et al. [6], recommended that development of standardized methods for disease diagnosis and screening of pathogens, along with regular evaluation of their effectiveness as compared with other diagnostic methods should be a priority task. Vaccination is another established, proven and cost-effective method for controlling certain infectious diseases in cultured marine animals. Vaccines decrease the severity of disease losses, reduce the need for antibiotic use, leave no residues in the product and do not induce pathogen resistance. In conjunction with good health management and good husbandry practices, there is great potential for the use of vaccine technology for specific use in marine aquaculture.

In this work, we have revised the main infectious pathologies affecting to both wild and reared gilthead seabream; and in addition, some pathologies provoked by physiological (i.e. nutritional disorders), not optimal or inadequate rearing or environmental conditions, and potential genetic factors have also been updated. Future perspectives on welfare, treatment and prophylactic measures to improve the Mediterranean aquaculture are also discussed.

Malformational and skeletal disorders

The presence of morphological abnormalities in reared gilthead seabream is an important problem for current aquaculture and it entails significant economic losses. Malformations can affect different aspects of the morphology of the fish such as pigmentation, shape, scales, skeleton and swim bladder. The high incidence of some malformations significantly reduces the market value of the species commercialized as whole fish and implies an additional effort at farms to eliminate abnormal fish [7]. The incidence of vertebral deformities, i.e. opercular anomalies can vary from 6 to 80% [8-14]. These noticeable quantitative variations can be attributed to several different variable zootechnnical conditions, optimization in the rearing procedures and feeding protocols, and the application of genetic improvement programmes (i.e. bloodstock selection and breeding) during the last two decades. Skeletal deformities are the most relevant malformations and they include head and vertebral column anomalies. Lack of operculum and lordosis, scoliosis, kyphosis and vertebral fusions are the most frequent skeletal anomalies in gilthead seabream, particularly in reared fish, but also in wild populations [15]. Similarly, a slight association with inbreeding has been reported on skeleton abnormalities by Astorga et al. [16], and in addition, Negrín-Báez et al. [14], reported inheritance of skeletal deformities in gilthead seabream, such as lack of operculum, lordosis and vertebral fusions, among others. Nevertheless, Castro et al. [10], reported only a slight familiar association when comparing seabream specimens lacking operculum, but neither between lordotics nor between normal ones and, they suggested that most phenotypic variation observed for lordosis and lack of operculum in gilthead seabream is due to environmental factors. Therefore, environmental conditions, nutritional imbalances and genetic factors or their interaction, is believed to be on the basis of most skeletal alterations *S. aurata* specimens [9,10,14,17-23].

Interestingly, by using histological, histochemistry and immunohistochemistry approaches, recently we have been registered two types of opercular anomalies in reared gilthead seabream specimens [13], which were described according to the classification previously reported by Beraldo et al. [24], Type I: the folding of the operculum (opercle and sub-opercle) into the gill chamber, starting at the upper corner of the branchial cleft and extending down to its lower third; and Type II: the partial lack of the operculum (lack of development of the opercle, subopercle, interopercle and preopercle) with a regression of the loose edge extending down to its lower third. The overall incidence of fish with deformed operculum was 6.3%. These opercular abnormalities unilaterally affected both sides of the head: the right (3.3%) and left (3.0%) equally; whereas the bilateral abnormality in the operculum only affected 1.1% of the reared fish. Fish with a severe external body shape deformity showed internal lesions characterised by an accentuated ventral curvature (lordosis) of the vertebral column. The degree of these pathological symptoms varied along the vertebral column axis and mainly affected vertebrae located between the limit of pre-haemal and haemal areas of the vertebral column (position 11 to 15 from urostyle upwards). The incidence of fish affected by lordosis was 10.1%. These histological and histopathological disorders indicated that the reduced opercular surface in the Type I deformity in gilthead seabream was mainly due to the folding of the edge of the opercle from the superior corner towards the gill chamber. The conservation of the different opercular bones that compose the operculum suggested an effect of the rearing conditions during sensitive developmental periods, coinciding with the beginning of skeletogenesis of the opercular complex, which is formed by intramembranous ossification from a condensed core of mesenchymal cells [24,25]. Considering that the supportive tissue of the operculum was not yet formed at this early developmental period, mechanical damage (i.e. excessive water movements) could cause this opercular malformation [26]. Nevertheless, in the opercular deformity (Type II) described in gilthead seabream specimens [13], the coalescence between opercular bone areas might have caused semi-rigidity and tissue fusion of the opercular structures, giving the appearance of underdeveloped or incomplete tissue. These opercular disorders might be mechanically induced by forced opercular movements occurring during ventilation or food ingestion processes [26], although the putative involvement of nutritional factors and/or environmental pollutants should not be negleted [7].

The aetiology of vertebral malformations in fish species is complex, multifactorial and still not completely known. Genetic, environmental, zootechnical and nutritional factors have been frequently associated with different or similar vertebral abnormalities in various fish species. Several authors indicated that vertebral deformities might appear during the notochord segmentation and vertebral centrum differentiation processes [22,27]. However, others suggested that these deformities are a consequence of disfunction in collagen metabolism at notochordal and perinotochordal collagen sheets during early development [28]. However, many vertebral deformities may also occur later in ontogeny, for instance during the ongrowing period, at which point they are generally induced by mechanical overloads [29], or by curvature of the vertebral axis [30], or by a combination of both situations [31,32]. According to Ortiz-Delgado et al. [13], in the affected vertebral region of the lordotic gilthead seabream specimens, a change in chondrocyte morphology, from vacuolated to hyper-dense, and an increased calcium deposition were evidenced, suggesting that a metaplastic shift was involved [33]. Furthermore, in these seabream lordotic specimens, a disorganization of the intervertebral region, with a complete loss of notochordal sheath integrity was evidenced. In addition, imbalanced cell cycling (proliferation vs. apoptosis) detected in deformed vertebral centra showing higher cell proliferation activity, which could explain the presence of dense packaged chondrocytes, occupying most of the intervertebral space without vacuolization. Moreover, a higher remodelling process may occur in lordotic specimens, such as was evidenced by using chondrogenic and osteogenic immunomarkers [7,13,34]. In general a preferential accumulation of osteocalcin in compact bone and notochord cells was detected in notochordal tissues of seabream specimens with deformed vertebrae. It is suggested that lordotic vertebrae should be more fragile that those normal fish with non-deformed axial structures.

A new type of vertebral malformation, named haemal vertebral compression and fusion haemal VCF), was described by Lozoides et al. [35]. It consists of deformed cartilaginous neural and haemal processes and the compression and fusion of vertebral bodies, affecting the posterior part of the vertebral column in combination with lordosis. The early anatomical signs of the haemal VCF consist of abnormal centrum mineralization, malformed cartilaginous neural and haemal processes and developing lordotic alterations. The histological examination of the deformed individuals reveals that haemal VCF is preceded by notochord abnormalities. In older animals suggests that haemal VCF is linked to high mortality rates.

Pathologies provoked by parasitic microorganisms

Parasitic diseases, also known as parasitosis, are infectious (or not) diseases caused or transmitted by eukaryotic organisms. Parasites can affect practically all-living organisms; however, many parasitic organisms do not cause diseases. They can induce stress and immunodepression, and as a consequence secondary infections, pathologies and severe disorders diseases, are more frequent in those parasited fish.

The most frequent parasites that affected during the last decade to reared gilthead seabream were *Amyloodinium* spp., *Cryptocarion* spp., *Ichthyobodo* spp. and *Trichodina* spp. [36,37]. In addition, these parasites are very good indicators of contamination in aquatic ecosystems. In fact, high rates of mortality and infestations about 80% in gilthead seabream specimens reared under highly stressed aquatic ecosystems have been scored, with presence of inorganic and organic contaminants [38]. Amyloodiniosis or "Velvet disease" is one of the most devasting parasitic diseases in temperate mariculture [39,40]. *Amyloodinium ocellatum*, a dinoflagellate protozooa highly adapted to parasitism, is able to infect different fish species in a wide range of salinities and temperatures (17 to 30°C). Its life cycle has three main phases: a parasitic feeding stage (trophont), an encysted reproductive stage (tomont), and a free-swimming infective stage (dinospore) [41]. Damages of the gill epithelium and osmoregulatory impairment are the likely causes of fish death. The dinospores are susceptible to various chemotherapies [41,42], but trophonts and tomonts are more resistant. Treatment with 100-200 mg/L formalin for 6-9 h detaches trophonts from fish, but as tomonts, they resume division after the removal of formalin [41]. A copper sulfate treatment (0.75 mg/L) for 14 d is also effective, although toxic for juvenile fish [41]. Survivor fish acquire a certain degree of immunity [43].

Cryptocaryon irritans (Class Colpodea) produced the "Marine White Spot disease", is a ciliate that invades the epithelium of gills, skin, and eyes, compromising the physiological functions of these organs. The clinical signs include pinhead-sized whitish "blisters" on the skin, epithelial hyperplasia, mucus hypersecretion, skin discoloration, corneal cloudiness, and mainly disruption of the gill lamellar structure and severe respiratory distress [40]. In Mediterranean cultures of *S. aurata*, the ciliate has been reported in Israel, Italy and Spain [44]. The life cycle of this parasite consists of four phases: the first is parasitic (trophont), after 3-7 d of growth, it leaves its host, loses its cilia (protomont), encysts, and starts dividing (tomont), eventually producing up to 200 free-swimming infective organisms (theront). Theronts have a life span of 24 h, but their ability to infect a host decreases rapidly after 6-8 h [45,46]. Studies on vaccination against *Cryptocaryon* have produced interesting results [47,48], but no commercial vaccines are still available.

Trichodina spp. has been observed often infesting the gills of reared seabream specimens and also in wild and culture sparids in Mediterranean and Atlantic areas [40,49-51]. *Brooklynella hostilis* is a ciliate easily recognizable by its oval, dorsoventrally flattened shape, by its notched oral area, and by its size [52]. As a gill pathogen, *B. hostilis* can cause serious skin lesions [4], destroying the tissue surface of the hosts by mean its cytopharyngeal armature, feeding on tissue debris, ingesting blood cells, and causing hemorrhages in the gills [52]. *B. hostilis* was diagnosed in cagecultured gilthead seabream in the Red Sea [53].

Microsporidiosis is a disease provoked by eukaryotic parasites belonging to the phylum Microsporidia. This phylum includes obligate intracellular parasites that infect a wide range of vertebrate and invertebrate hosts. Microsporidians have evolved an elaborate mechanism for invading animal host cells, but have otherwise greatly reduced biological complexity. Although the taxonomic affiliation of the Microsporidia has long been controversial, they are now known to either fall within the Fungi or to be extremely closely related to the Fungi [54,55]. Economic losses were recorded in aquaculture due to microsporidian infection of fish [55], establishing a complex coexistence with the host, for example, the genus *Glugea* develops a special type of hypertrophy forming a xenoma, several of which may aggregate into a large pseudotumoral structure, the most adequate treatment is the oral administration of fumagillin [4,55]. In the Mediterranean region, a microsporidian infection was described in juveniles of cultured gilthead seabream in the French coast attributed to *Glugea* sp. [56]. Abela et al. [57], observed lesions by microsporidian parasites (genus *Pleistophora*) in the muscle of cultured gilthead seabream juveniles, and xenome-infections in *S. aurata* provoked by *Microsporidium aurata* was also reported by Morsy et al. [58], in the Red Sea. Similar cases of microsporidian infections in the musculature of gilthead seabream have been reported in Greece [59], Italy [60], and Spain [40,61].

Piscine apicomplexans, belonging to the classes Coccidea and Haematozoa, can parasitize a broad spectrum of fish cell types in the intestine, swim bladder, liver, spleen, testes, kidney, gills, and blood [62,63]. Since coccidiosis provoked in fish subclinical and/or chronic diseases, they may have been overlooked. However, haemogregarine-like organisms were observed in gilthead seabream cultured in Israel [64]. *Eimeria sparis* and *Goussia sparis* were recorded in the intestine of gilthead seabream in different facilities in Spain, indicating a wide distribution and a potential responsibility in mortalities [49,65,66]. *Cryptosporidium molnari* is another species described in gilthead seabream, detecting in its gastric epithelia, with a particularly high prevalence in juveniles [67-70]. Affected fish showed abdominal swelling, ascitis, whitish feces, and with necrosis of the gut epithelial lining. *In vitro* treatment with bronopol (100 mg/L for 30 min) has demonstrated to be effective, killing 50% of theronts and 100% of protomonts [71].

Myxosporeans are endoparasites that either can reside in visceral cavities such as the gall bladder, the swim bladder, and the urinary tract (celozoic species) or can settle as inter- or intracellular parasites in the blood, in muscle, or in connective tissue (histozoic species). The myxozoans are included in three orders Malacovalvulida, Multivalvulida, and Bivalvulida [72]. The main myxozoans that affect to fish specimens are the genera *Myxobolus*, *Ceratomyxa*, *Enteromyxum* and *Sphaerospora* (Bivalvulida), genus *Kudoa* (Multivalvulida), and genus *Tetracapsuloides* (Malacovalvulida) [73,74]. Infected fish do not always display clinical signs; in fact, an important number of myxosporidian parasites coexist with their asymptomatic host without causing obvious damage [75]. Spores typical of the genus *Kudoa* were found in the viscera of gilthead seabream cultured in the Red Sea [76], but this parasite causes relatively benign infections, one usually limited to a few individuals. However, under some particular stress conditions or when highly pathogenic species (*Ceratomyxa shasta*, *Myxobolus cerebralis*, *Tetracapsuloides bryosalmonae*) are involved, virulence is enhanced and expressed. General clinical signs are often emaciation, swollen abdomen, and gall bladder full of unreleased bile. Most myxozoan infections elicit only moderate host reactions at least during the early stages of infection, although plasmodia with mature spores can later induce considerable inflammation [4]. *Enteromyxum leei* (formely *Myxidium leei*) and other enteromyxosporidan parasites are one of the major disease problems in marine aquaculture, since the infection has a chronic course. Affected fish become anorexic and emaciated, and eventually die with a typical “knife edge” body shape and bloated abdomen, and the extensive necrosis of the intestine produces a foul odor. Following the first report and description of *E. leei* in cultured gilthead seabream from Cyprus [77], the parasite was found associated with morbidity and mortality in Israel [78], Greece [79-81], France [82], Italy [83], Spain [84], and Tunez [37]. In gilthead seabream, the infection shows variable incidence and severity, possibly indicating a genetically based susceptibility to the disease [74], and direct transmission [85]. Other myxosporean parasite, *Polysporoplasma sparis*, has occasionally been associated with poor growth and chronic mortality, affecting mainly to glomerular capillaries of the kidney (glomerular disease) [86]. It was reported in Spain, in the Adriatic Sea, and in fish farms all over Greece, with high prevalence during the warmest season [81,86-89]. *Enterospora nucleophila* is a microsporidium responsible for an emaciative syndrome observed in farmed gilthead seabream. The parasite is mainly found in the intestinal mucosa with clinical signs including anorexia, cachexia, and pale internal organs [57]. Several histopathological damages occur in severe infections and this microsporidium is considered a serious emerging threat in gilthead seabream production [61]. According to Martins et al. [90], three applications of formalin solution (10 mL/m^3) for 15 d were adequate to control the disease caused by the protozoa. Cellular effectors (lymphocytes, granulocytes, phagocytes, non-specific cytotoxic cells, and rodlet cells), and also humoral factors (lysozyme, peroxidases, antiproteases, complement, and specific antibodies) seem to be the main fish immune components involved in the response against myxosporoses [91].

Class Monogenea is comprised of mostly ectoparasites fluxes, the most frequently encountered worm in mariculture [92]. Flukes either draw or feed off the host tissues, causing irritation, hyperplasia, haemorrhage and anaemia. *Furnestinia echeneis* is frequently observed on gilthead seabream in the Mediterranean [93], and they are usually presented at the distal extremities of the gill lamellae [94,95]. The rates of infestation are very low, depending on the temperature [96], and the fish appareared to be in good health and no evident symptoms were exhibited [97]. *Sparicotyle chrysophrii* is other common monogenean parasite for cultured gilthead seabream [92,94,98], and its haematophagus activity produce severe anaemic conditions in the cold seasons [97]. *Gyrodactylus* was found on the fins and body surface of gilthead seabream cultured in several Mediterranean regions [40,92]. Other monogenoidean parasites detected in gilthead seabream are the belonging to the species *Encotyllabe vallei*, *Lamellodiscus echeneis*, *L. ignoratus*, and *Polylabris tubicirrus* [92]. A 1-h formalin treatment (150-200 mg/L) or hydrogen peroxide (200 mg/L, 30 min) are good methods of treatment. Eggs, however, may survive the therapies, so that repeated treatments may be required to disrupt these parasites. *Neobenedenia melleni* is very sensitive to freshwater and, a 3-min freshwater dip is normally sufficient to free the fish from this infestation, but, the eggs may also survive the treatment [40]. Recently, Chagas et al. [99], have described that the supplementation of the diet with mebendazole controls the monogenean infestations in the freshwater fish *Colossoma macroporum*.

Class Digenea, such as *Monorchis monorchis* and *Telosentis exiquus*, comprises endoparasitic platyhelminths that require at least one intermediate host to complete their life cycle. In *S. aurata*, the parasite *Bucephalus minimus* has been found as encysted larval or juvenile stages, and as free adults [100], and *Neobenedenia melleni* has been detected on the body of gilthead seabream cultured in the Red Sea [101]. Acute infections by the cercariae have occasionally been observed due to severe damage in the host tissues during penetration and migration because the active feeding of the monogeneans on mucus and on epithelial cells leads to hemorrhage, inflammation, and the over-production of mucus [102,103]. Parasites often settle on or around the eyes, damaging the cornea and causing blindness [103,104]. Once encysted, metacercariae do not produce further tissue damage, except intense melanization reaction around the cyst. *Cardicola aurata* were reported affected gilthead seabream in Spain, Italy, Croatia, and Greece [60,105]. Massive presence of eggs and miracidia caused clogging of the gill capillaries and severe local tissue damage, while the adult individuals could be found in the vessels of the renal parenchyma or in the afferent vessel of single gill arches [106,107].

A large number of copepods belonging to the families *Caligidae* and *Ergasilidae* parasitize the itegument of fish [108]. Gill filaments can be severely damaged and skin haemorrhages typically occurring in heavily infestations, although copepod presence on *S. aurata* has only rarely been associated with fish mortalities [97]. Several treatment agents have been suggested for control of copepods, including formaldehyde, organophosphate insecticides, hydrogen peroxide, ivermectin, pyrethrum, carbaryl, diflubenzuron, to name a few. However, the therapeutic dosage may be toxic for the hosts, and other measures, such as exposures to freshwater, are applied. Family *Cymothoidae* constitutes the great majority of isopod parasites in fish [109]. These parasitic isopods are grossly visible on skin, mouth and gills of the infected fish, causing considerable damages [110]. In addition, *S. aurata* is susceptible to the larvae of the *Gnathiidae* family, of which *Gnathia piscivora* constitutes a potentially dangerous risk [111]. The most common isopod affecting gilthead seabream in the Mediterranean are *Ceratothoa paralella* [112] and *C. oestroides* [113,114].

Bacterial, viral, and fungi pathologies

Vibrio spp. has been isolated frequently from diseased gilthead seabream in several farms around the Mediterranean basin [115]. Mortalities of cultured gilthead seabream were associated with *V. alginolyticus*, *V. parahaemolyticus*, *V. vulnificus*, *V. harveyi, V. ordalii*, *V. salmonicida,* and *V. anguillarum* [40,116-121]. Vibriosis is characterized by a systemic hemorrhagic septicemia. Lethargy, skin darkening, exophthalmia, anemic gills, petechia on the skin and the base of the fins, and inflammation and ulcers are the typical external signs. Internally, congested visceral blood vessels, intestinal hemorrhages, and accumulation of ascitis fluid in the abdominal cavity are the most common signs of vibriosis [122,123]. *Vibrio* spp. produces a wide variety of proteases, hemolysins, and other extracellular enzymes that are responsible for the extensive tissue damage [124]. In advanced cases, congestion and liquefaction of the spleen, liver, and kidney can also be observed. Factors such as transport stress, water temperature changes, handling, and low oxygen induced vibriosis in *S. aurata* [125]. Treatment of vibriosis with medicated feed can be effective if done at the initial stage of the disease, while the fish are still eating. Flumequine, oxytetracyclines, sulfonamides (+ trimethoprim) and florfenicol are the main antimicrobials used for vibriosis treatment. Vaccination as preventive measure is the best option since its effectiveness has been demonstrated about 100% during the protection period using both immersion and injection procedures. Oral formulations with good effectiveness are strongly required by the industry because could help reducing handling and improving welfare, but they are not enough developed. Good animal husbandry and adequate nutrition are essential to prevent the development of the disease and, subsequently, the use of antibiotics. Combination of the suitable and available vaccination protocols has a real benefit in cost-effect balance. The emerging crisis of resistance to antibiotics has led to sporadic application of probiotics in *S. aurata* culture [126], in order to develop immunocompetance in fish to combat with bacterial diseases and also inhibit the colonization of potential pathogens in the digestive tract through competition exclusion principle. However, in general probiotics are low immunogenic in nature, temperature- and salinity-sensitive and cumbersome in application. Phage therapy can be described as the use of bacteriophages to control specific pathogenic or problematic bacteria. Experimental results with marine animal models have demonstrated the efficacy of phage therapy against infectious diseases caused by *Vibrio harveyi*, *V. parahaeamolyticus, V. anguillarum*, and *V. alginolyticus* [127-130].

Photobacteriosis is provoked by two subspecies of *Photobacterium damselae*, one of them *P. damselae* sub sp. *piscicida* caused the "pseudotuberculosis" that is recognized as granulomatous-like lesions in the spleen and kidney of affected fish. This disease develops rapidly into an acute septicemic condition characterized by conspicuous splenomegaly, and high mortalities have been observed in gilthead seabream from Atlantic and Mediterranean areas [118,131-135]. Transmission of the pathogenic bacteria can be vertical, through the gonadal fluids, as well as horizontal through the water route, by this route the bacteria is able to infect its host through the gills, the digestive system and the skin [131,136]. The other subspecies of *P. damselae* is *P. damselae* subsp. *damselae* (formerly *Vibrio damsela* or *Listonella damsela*). This microorganism causes skin ulcers or systemic disease in a wide range of fish, including gilthead seabream [137-140], and can also cause skin ulcers in humans [141]. Antibiotics have been the first line of defense in fish aquaculture to control photobacteriosis outbreaks, but after only a few years the pathogens acquired resistance to various antibiotics, such as kanamycin, sulphonamide, tetracycline, ampicillin, chloramphenicol, florfenicol, and erythromycin [142]. Efforts have been focused on gaining a better understanding of the biology of these pathogenic microorganisms with the aim of developing effective vaccination strategies to control the disease. Conventional vaccinology has thus far yielded unsatisfactory results, and recombinant technology has been applied to identify new antigen candidates for the development of subunit vaccines [142].

Pseudomonas anguilliseptica infections have been described in gilthead seabream [143] associated with a hemorrhagic septicaemia named "winter syndrome" or "winter disease" (WD) [40] in the Mediterranean areas. WD refers to a condition exclusively affecting gilthead seabream reared at low temperatures. The disease is considered as a multifactorial problem brought about by the physiological, metabolic, and immunological disturbances associated with the poor tolerance of this species to rearing conditions at temperatures below 15°C [144-148]. Although the WD is probably multifactorial with unresolved aspects of its etiology, the recurrent isolation of *P.*

anguilliseptica of WD-afeccted fish indicates a significant role of this microorganism in the disease [143,149,150]. External signs included a moderate abdominal distension and keratitis, anemia, lethargy and fish become darker and with the typical stress bands, and sometimes petechial haemorrhages on skin [143]. Internally, hepatic pallor and severe distension of the intestines are evident; usually the diseased fish develop meningoencephalitis. The fish mortality of this disease is higher in the second stage (early spring at 15-16°C), where *P. anguilliseptica* is recorded frequently [143,149,150]. Treatment with ciprofloxacin, erythromycin, gentamycin, oxytetracycline, tetracycline, streptomycin or trimethoprim-sulphamethoxazole gives a good response [151-153]. Recently, Phumkhachorn & Rattanachaikunsopon [154] used a bath treatment with extract of the plant *Cassia alata* to control the *P. anguilliseptica* infection. There are no commercial vaccines available for this disease agent, although several experimental vaccines have been tested [151,155,156].

Tenacibaculum maritimum [157] is a bacterium commonly found in seawater and formerly known as *Cytophaga marina* or *Flexibacter marinus* or *F. maritimus*. It is an opportunistic pathogen responsible for "flexibacteriosis," also known as "gliding bacterial disease," "eroded mouth syndrome," and "black patch necrosis." Flexibacteriosis was described in Europe, USA, and Japan affecting mainly to larval or juvenile of a high variety of fish species. An increase in water temperature, various stressors and skin abrasions may trigger the development of the disease. The mouth appears eroded and hemorrhagic, lesions may open in the skin, fins and tail appear frayed, and foci of gill rot may develop followed rough handling during grading and other netting procedures in nurseries [40]. The disease can become systemic, involving different internal organs. *T. maritimum* has been described in gilthead seabream associated with coinfection with monogenean gill parasites (*Sparicotyle* and *Furnestinia*) [158,159]. *In vitro* studies on the susceptibility of *T. maritimum* to various chemotherapeutic agents indicate that all bacterial strains isolated from different sources exhibit a similar pattern [158], but field results were not always similar [160]. The administration of amoxycillin and trimethoprim and enrofloxacine are effective antimicrobial therapies against this pathogen in field trials [158,161]. An alternative to drugs would be the use of surface-acting disinfectants administered by immersion, such as formalin, potassium permanganate, and hydrogen peroxide [158]. Modifying husbandry parameters (temperature and/or salinity, controlling fish densities, reducing stress conditions, and avoiding overfeeding) decrease the occurrence of tencibaculosis in fish farms [158,162]. To date, there is a general agreement that a vaccine would considerably help to control tenacibaculosis and several research programs have been established [163], although at present, only one bacterin is commercially available to prevent turbot mortalities caused by *T. maritimum*, but may not be effective in preventing the tenacibaculosis in other fish species [164]. Other vaccine developments are under trial experimentations yet [155,165].

Epitheliocystis is an infectious disease caused by the obligate intracellular bacteria *Chlamydia*, and it was described in cultured gilthead seabream in Israel [166,167], in Italy [168], and in Spain [94,169]. Co-infections with other fish pathogens, such as monogeneans, *Trichodina* and *Vibrio* spp. have been reported by several authors [50,169]. Nevertheless, recently similar epitheliocystis disease that affected to gilthead seabream specimens was associated with intracellular beta-proteobacteria agents, such as *Ichthyocystis hellenicum* and *I. sparus* [170]. Epthyteliocystis appears to be a seasonal disease in Mediterranean farmed gilthead seabream, occurring during the warmer months and when juveniles are first introduced into seacages. However, epitheliocystis outbreaks have occurred in aquaculture systems associated with high stocking densities, presence of nutrients, season, temperature and fish age [171]. Since more than one organism might be involved in an outbreak and since diagnosis can be problematic, there is no established treatment for this pathology. Alternative husbandry methods, such as decreasing stress factors and increasing water quality, around the time of outbreaks times has been recommended [172], together with ultraviolet irradiation of water supplies [173]. Antimicrobial therapy has been attempted in control of this microbial pathogen, using tetracycline and macrolide antimicrobials [174]. However, Somridhivej et al. [175], demonstrated that water exchange was the most appropriate treatment to treat the disease or mitigate the heavy infection.

Lymphocystis disease (LCD) is a well-known fish viral infection provoked by a DNA virus (LCDV) belonging to the *Iridoviridae* family [176], which is characterized by hypertrophy of fibroblastic cells in the dermis connective tissue of affected fish, occasionally proliferating as true epithelial tumours [177]. This viral disease affects a wide variety of fish species, including *S. aurata*. Paperna et al. [178], reported for the first time the occurrence of LCD in gilthead seabream reared in the red Sea, but imported as fingerlings from Mediterranean Sea. Later, this viral disease was disseminated to several aquaculture nurseries around Mediterranean basin, where the virus probably become endemic, including Italy, Spain, Greece, Turkey, France, and Portugal [179-186]. Although this disease is rarely fatal, fish showing the characteristic symptoms cannot be commercialized, causing important economic losses [179]. The main characteristic of LCD is the appearance of small cream-coloured nodular lesions on the fish skin and fins [187,188]. Each nodule consists of an LCDV-infected cell, named lymphocyst or lymphocystis cell, of up to 1 mm in diameter [178]. These hypertrophied cells may occur singly or grouped in raspberry-like clusters of tumour appearance. These cellular aggregates are usually whitish in colour, and in heavily affected fish, lymphocysts may cover the entire body, spreading from the gills to the fins [178,182,189,190]. Less frequently, they have also been described on eyes, causing exophthalmia, and internally over the mesenteries, peritoneum and several internal organs [187,190,191]. LCD is a chronic and self-limiting disease that, depending on the host fish species and environmental conditions, may persist for a variable period of time [192]. Thus, the LCD-associated lesions may be evident for 1 year in cold-water fish, whereas they disappear after several weeks in warm-water species [178,193]. There is no effective therapy for LCD; reduction in stocking density and the removal of heavily infected individuals are the only measures that can be adopted to reduce the impact of this disease [194]. The maintaining LCDV-free populations should be prioritizied for sustainable aquaculture in endemic areas [195]. Vaccine against LCDV has focused on the development of a recombinant plasmid DNA vaccine with a fragment of the major capsid protein into an expression vector [196], the plasmid is expressed in fish and induced a specific immune response [197-199]. Another experimental vaccine using encapsulated microspheres loaded with pDNA coded for LCDV showed efficacy after oral administration [200].

The Viral Nervous Necrosis (VNN) or Viral Encephalopathy and Retinopathy (VER) is a viral fish disease provoked by the Nervous Necrosis Virus (NNV) belonging to the family *Betanodaviridae*. Pathogenesis of VER is related to the neuro-invasive nature of the virus and its deleterious effect on tissues in the brain and retina. Clinically, VER is characterized by nervous symptoms, such as impaired coordination, loss of balance, whirling swimming, blindness with consequent changes in pigmentation, swim-bladder hyperinflation, and hyperexcitability in response to noise and light. Other general signs are lack of appetite, lethargy, and anemia. Mortality may reach 100%, in particular in larval and juvenile stages, within 1 week from the onset of the neurological symptoms, depending also on the viral genotype. Chronic, asymptomatic infection of VER is also frequent in older individuals, and it is transmitted both vertically and horizontally routes. NNV has been detected from gilthead seabream farmed in Greece, France and Spain, [140,201-205]. Although, *S aurata* harbours the virus and acts as an asymptomatic carrier [206], recently it has described the disease affects to this fish species [207,208]. No chemotherapy is available for VER, therefore control depends upon husbandry practices that prevent contact between naïve and infected fish within farms and also between different geographical areas. Ozone has been used to avoid or reduce virus contamination on egg shell surface [209], and virus contaminated water may be effectively sterilised by UV exposure [210]. Different studies have shown that immunisation using recombinant viral coat protein expressed in *E. coli* or virus-like particles expressed in a baculovirus expression system or formalin-inactivated virus may be effective in controlling the disease [211-213]. Yamashita et al. [214], showed that primary infection with an avirulent aquabirnavirus effectively suppressed secondary betanodavirus infection, suggesting the use of the aquabirnavirus as a potential immunomodulator. Recently, several DNA-based vaccines have been developed against NNV [215,216].

Only a few fungic infections have been reported affecting *S. aurata* farmed in Mediterranean basin [217-219]. *Ichthyophonus* spp. causes ulcers and granulomatous lesions in internal organs. Lesions are most common in highly vascularized organs (spleen, kidney, heart, and liver), and the infection to have a chronic course, and prevalence seems to increase with host age [220,221]. The potential infection from wild fish species should not be underestimated since any effective treatment has been devised so far [221]. Abdel-Latif et al. [222], reported that the most prevalent fungi detected in cultured *S. aurata* in Egypt were species of *Aspergillus*, *Cladosporium*, and *Fusarium*.

FUTURE PERSPECTIVES

Diseases have proved major constraints to efficient production in intensive culture of gilthead seabream in Mediterranean areas. Major improvements in the understanding of the aetiology and epidemiology of this fish species pathologies have been achieved in recent years; and, therefore, fish farmers in several Mediterranean countries have significatively improved their husbandry practices with greater focus now on fish welfare. Control of many serious infectious diseases has been achieved through new chemicals and vaccines, and this is especially true for bacterial diseases. However, new pathologic problems are emerging, and previously rare diseases becoming much more prevalent; therefore, continued vigilance and solution development is required.

Due to the complex set of interactions that facilitate the spread of disease, multi-level interventions are necessary. Farm-level disease interventions, such as timely diagnosis and treatment, could address the host-pathogen relationship, while improved farm management may address environment-pathogen and environment-host issues. To address disease transmission between farms, regional and national policies, surveillance, reporting, training, and emergency response capabilities are also needed.

Developing and promoting production methods that reduce or eliminate the need for antibiotics, pesticides, and other chemicals, which can have wide-ranging impacts on human, fish, and environmental homeostasis is a need for a sustainable practice of aquaculture. For this, viral vaccines, based on the recombinant DNA technology and subsequently direct DNA vaccination, appear to be very promising. As this involves a transfer of genes, there are significant issues of safety and consumer acceptance to be addressed. Another approach showing promise is the use of proteomics and epitope mapping for the identification of vaccine antigens and the subsequent development of peptide vaccines, which might be appropriate against parasitic diseases. Further methods include the use of virus-like particles or recombinant viral proteins produced in yeast will potentially be use to pathogen control.

New therapies using genomic tools appear to be promised, for example using dsRNA for disease protection and RNA-i-based gene therapies. Antimicrobial peptides are also being studied as a potential therapeutant. Aquaculture diets are also under scrutiny with respect to potential for delivery of immunostimulants and better understanding of interactions between gut microbiota, pathogens and micronutrients, including probiotic effects.

In short, this review has shown that there is a substantial scientific and empirical base for the implementation of Integrated Pathogens Management Strategies (IPMS) in *S. aurata* farming, and that nowadays integration of all the available preventive and treatment strategies is indispensable to fighting the diseases of this fish species.

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Cite this article

Borrego JJ, Labella AM, Castro D, Ortiz-Delgado JB, Sarasquete C (2017) Updated of the Pathologies Affecting Cultured Gilthead Seabream, Sparus aurata. Ann Aquac Res 4(2): 1033.