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Review

Microbial Interactions That Contribute to Gill Disease in Aquaculture

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Abstract: The rapid growth in the human population has led to an increased requirement for readily available food sources. The aquaculture industry is a fundamental source for maintaining food supplies; however, it is subjected to mounting pressures to meet supply demands. Thus, limiting factors that negatively impact the cultivation of farmed aquatic organisms is essential. Gill disease is an increasing area of concern, resulting in substantial losses in farmed fish. Several microbial pathogens are known to cause gill disease and, in many instances, multiple pathogens or factors can be involved in the disease, resulting in complex gill disease (CGD). The role of mixed infections in gill disease is largely unknown, as such this review aims to examine data on previous infections and highlight the variety of microbes that might be involved in gill disease. The influence of climate change in the context of CGD is also discussed given the strong links between physicochemical extremes and numerous microbial gill pathogens. Understanding these factors will allow for improved diagnostic and therapeutic strategies to be implemented.

Keywords: gill disease; complex gill disease; amoebic gill disease; aquaculture; pathogen

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1. Introduction

A large proportion of the aquaculture industry is dedicated to the cultivation of fish species, such as Atlantic salmon (*Salmo salar*) and rainbow trout (*Oncorhynchus mykiss*) and maintaining good fish health in these environments is a complex and important task. Gill health is an increasing focus for the aquaculture industry as fish loss to gill disease (GD) impacts on economic costs [1].

Fish gills are multifunctional and important in performing gaseous exchange, osmoregulation, excretion of nitrogenous waste, pH regulation and the production of hormones [2], and injury or infection of these can prove fatal to the fish. As fish and their gills are directly exposed to the marine environment, there are constant opportunities for the gills to be invaded by pathogens and/or damaged by toxins and, as the gill is physically delicate and permeable, this structure is further susceptible to harm from external factors [3]. GD is increasingly common in the aquaculture industry and its prevalence relates to several different pathologies, different causative pathogens, and can be influenced by a range of environmental variables or events [3–5]. With both pathogenic and non-pathogenic forms of disease, there is significant financial stress on the aquacultural industry with a predicted losses of $84 million in the US annually [6], and 5.8–16.5% of the total earnings within the UK [7].

Farmed fish are exposed to a plethora of different microorganisms, with numerous microbial interactions occurring. Host-associated microorganisms are typically termed the 'microbiome'. Dysbiosis in the gill microbiome has shown to contribute to GD pathology [8], but it is important to recognise that the environment in which fish live consists of a variety of additional parameters which initiate susceptibility to infection. This can include chemical constituents, salinity, pH, temperature, and dissolved oxygen levels [9–13], which in turn can create a stressful environment for teleosts [9,10,14]. If the fish become stressed, have

underlying health issues, are exposed to physical damage or immunosuppression [15], microorganisms associated with the reduced health status of the host compose the 'pathobiome' [16]. As there are different causes of GD, and cases are often multifactorial, it is important to consider the nature of the pathobiome in diagnosis and treatment. In recent years, this has extended to include changes in additional environmental parameters, such as salinity, pH and temperature, particularly with climate change known to influence these factors [1,17]. Many microorganisms of the pathobiome interact with each other, as well as the host, some live as symbionts with other microorganisms, or have been simultaneously isolated with suspected causative agents, potentially causing co-infection. For example, predatory protist species such as amoebae, have been shown to harbour phagocyte resistant bacteria and as such can act as a vector to other opportunistic pathogens [18]. Indeed, several *Vibrio* species can survive within *N. perurans,* the causative agent of amoebic gill disease (AGD) and the impact of this relationship on virulence and survival of the amoebae is unknown [19].

The multifactorial nature of GD makes it difficult to diagnose and treat. In addition, the isolation of multiple potential pathogens from diseased gills can obscure diagnosis, treatment, and research. This review aims to emphasize the importance and diversity of microbial interactions in gill diseases by identifying key pathogens and discussing their influence on disease severity, highlighting the potential pathogenicity of microorganisms causing infectious GD and evaluating the impact of climate change on microbial abundance, species prevalence and their subsequent interactions.

2. Infectious and Complex Gill Disease

There are many types of infectious and non-infectious GD cases reported in marine aquaculture where the specific causative agent or pathogen has been isolated and identified [4]. However, there are an increasing number of cases where the cause of GD is either multifactorial or non-specific, termed 'Complex Gill Disease' (CGD). CGD is commonly observed in farmed teleosts and involves multiple putative pathogens, with mixed aetiologies, occurring simultaneously [20].

Several species of economically important farmed teleost are susceptible to GD such as salmon (including Atlantic, chinook, coho [12,21–25]), turbot [24,26], trout (rainbow [22,25] and brown [27,28]) and increasing incidences have been documented worldwide [4,21,23,24,29,30]. This increase has been linked to changes in environmental factors; studies on AGD, caused by the opportunistic pathogen *N. perurans* [31], have determined that environmental factors such as temperature maximums [13,30,32], periods of low rainfall [22,30] and increased infective load within the environment affect both host and associated microorganisms [14,33]. Importantly, these are all parameters that are increasing in prevalence as a result of climate change [34–36]. Additionally, farming site practises also play a role in the development of disease, e.g., biomass of fish within cages, cage distribution, cage cleanliness [12,15,37,38]. These factors can influence fish stress levels, compromising their immune systems and thus, leaving them vulnerable to further infection [15,39]. Additionally, host specific attributes, e.g., genetics [39] and size [40] have been observed to contribute to disease onset and progression [41,42].

As these infections cause a wide range of chronic proliferative and inflammatory problems in the gills, the gills and immune system of the host are more susceptible to further infection from opportunistic pathogens, causing simultaneous gill problems [3,5,43]. GD can occur from numerous causes, i.e., from specific bacterial infections, such as *Flavobacteria* [29,44,45] or *Aeromonas* [46,47] and parasitic infections from various causative species such as *N. perurans* (AGD) [48,49], *Desmozoon lepeophtherii* [50,51] and *Ichthyobodo* spp. [52,53].

Whilst efforts are made to identify a causative pathogen and provide a diagnosis during infectious gill disease, evidence is emerging that multiple microorganisms and their interactions may be concurrently responsible and the interactions between the varying organisms may contribute to the severity of infection and disease resolution [3]. During

CGD histological examination shows epithelial cell proliferation, necrosis, inflammation (presence of sub-epithelial inflammatory cells) [54] and vascular changes (lamellar haemorrhage/thrombosis) [3,55,56]. External pathologies include increased mucus secretion [4], swollen/shortened gill filaments [3] and fusion of lamellae [4,57]. Skin haemorrhages and/or loss of scales have also been reported in some cases of fish suffering from proliferative gill inflammation, although it is unclear whether these are linked [58]. Behaviourally, fish may swim close to the surface and crowd, as well as display signs of lethargy, loss of appetite and increased respiratory rate [3,57,59,60]—these symptoms are consistent and recurring during GD.

The identification of a primary pathogen is necessary during GD, as effective and timely treatment is critical to host survival [15]. Due to challenges in diagnosis, the umbrella term 'Complex Gill Disease' has now come to encompass independent marine gill diseases such as Salmon Gill Poxvirus Disease (SGPVD) [61], Ichthyobodosis/Marine Costiasis [56], Tenacibaculosis [62] as well as multifactorial infections such as Epitheliocystis [57,63,64], Amoebic Gill Disease (AGD) [8], Proliferative Gill Inflammation (PGI) [65] and Proliferative Gill Disease (PGD) [66] and independently, these diseases present certain distinguishable aetiologies which may help identify primary pathogens during CGD. For example, in Salmon Gill Poxvirus infections, histopathology assessment of the gill tissues commonly reveals apoptosis of gill epithelial cells, leading to acute lamellar collapse or chronic gill epithelial hyperplasia. In some cases, the virus may infect other epithelial cells (oral cavity) and/or infect kidney function and clinical signs during SGPVD may present in erratic swimming behaviours [59,67]. In epitheliocystis the formation of cyst-like inclusions in the branchial epithelia of the host can be found and is caused by various intracellular bacteria [68]. Clinical signs may include lethargy and flared opercula as well as visible gill lesions [63]. Ichthyobodosis/Costiasis (caused by *Ichthyobodo* species) has been shown to cause acute hyperplasia and fusion of the secondary lamellae [56]. Increased melanin levels have also been observed external to the blood vessels of the primary lamellae and increased numbers of goblet cells can be seen in the secondary lamellae of infected gills [56]. External pathologies are also witnessed with Tenacibaculosis (caused by *Tenacibaculum* spp.) through the presence of ulcers, haemorrhagic and necrotic lesions/corrosion of the skin, fins and tail and haemorrhagic mouth [69]. AGD (caused by *Neoparamoeba perurans),* can be detected by observing white mucoid patches visible macroscopically on the gills [22], and with a histopathology assessment of gill tissues where hyperplastic lesions and associated amoebae are present [48] as well as fusion of lamellar [70]. Finally, both Proliferative Gill Inflammation (PGI), a non-defined syndrome or disease which causes hyperplasia and inflammation of the gills, and Proliferative Gill Disease (PGD), a non-defined syndrome or disease which causes hyperplasia but no apparent inflammation in the gills, are multifactorial conditions. PGI is associated with *Desmozoon lepeophtherii,* epitheliocystis and Atlantic salmon paramyxovirus (ASPV; Table 1) and PGD occurs in non-specific marine environments (fresh water PGD is associated with *Henneguya* [71]). In cases of PGI where *Desmozoon lepeophtherii* is present, there can also be distinct changes where spores are seen within the cytoplasm of lamellar epithelial cells [72].

Microbial Interactions in Gill Disease with a Focus on AGD

Pathogens that cause infectious GD are under scrutiny in an attempt to understand their pathogenesis, virulence factors and control measures [61,73–76] and are summarised in Table 1. However, it is also important to understand their role within microbial communities and this will enable further insight into why they cause disease and how diagnostics and fish health can ultimately be improved. For example, in AGD, the causative amphizoic amoebae, *N. perurans* are normally free-living predators of bacteria [19] making it important to understand the role of *N. perurans,* not only as a pathogen in AGD, but as a vector for other potential pathogens. Several bacterial species can evade phagocytosis in amphizoic amoeba species [18], including *N. perurans*, potentially leading to increasingly complex disease pathologies, which hinder accurate diagnosis [19]. Other amoebae have been

isolated from diseased gills (Table 1), but little is known as to whether they are involved in gill infection. Different *Neoparamoeba* (and/or *Paramoeba* species) have been isolated from cases of AGD. These include *N. pemaquidensis* [27] and *N. branchiphila* [77] and whilst their role and characterisation in GD remains uncertain, the examination of subtle differences in the genomes and transcriptomes of virulent and non-virulent species of *Neoparamoeba* could highlight key factors involved in pathogenesis [78].

During AGD, *N. perurans* attaches to the gill via the mucosal layer covering the epithelial surface [76]. In response to infection, mucus composition is altered on the gill, and production is increased to limit amoebic load [23,79]. Paradoxically, this could potentially aid the adherence of *N. perurans* to the epithelial surface and act as a nutrient source during infection for *N. perurans* and potentially its associated bacteria. *N. perurans* possess mucosal binding proteins and are capable of secreting proteases with mucolytic activity allowing evasion of the mucosal immune response and permitting infection [76] and putatively facilitating the establishment of other infections. Several species of bacteria have been frequently recovered from fish diagnosed with AGD (Table 1). For example, *Tenacibaculum dicentrarch* was positively associated with *N. perurans* presence in AGD biopsies in Australia [8]. Similarly, in Tasmania, *Psychroserpens* species were only identified in AGD-positive samples suggesting a possible opportunistic co-infection with *N. perurans* [33,80]. In addition, exposure trials found that the presence of *Winogradskyella* species during *N. perurans* infection resulted in a higher disease severity relative to *N. perurans* only control infections [81]. During an AGD exposure trial, *Winogradskyella* caused a significant increase in the percentage of AGD-affected filaments compared with controls challenged with *Neoparamoeba* only; however, these percentages did not increase significantly with an increase in bacterial concentration [82].

Vibrio species can be found intracellularly within *N. perurans*, potentially existing in a symbiotic manner [19]. The role (if any) they play during AGD infection remains to be investigated. *Vibrio harveyi*, an endosymbiont in *Cryptocaryon irritans*, the causative agent of marine cryptocaryonosis, can cause secondary infections [83] and the oyster pathogen *Vibrio tasmaniensis* interacts with an amoeba belonging to the Vannellidae family (where *Vibrio* evaded grazing by amoebae [84]). Thus, the survival of *Vibrio* within *N. perurans*, and other gill colonising amoebae, should be considered in understanding its role in AGD. *Neoparamoeba* spp. also contain a kinetoplastid-like endosymbiont (named *Perkinsela*-like organism; PLO) in close relationship with their nucleus that appears obligatory to amoebic survival [85–87]. The obligate endosymbiont itself is related to an ectoparasite of fish, *Ichthyobodo necator* [86] and for this reason, it is thought that the structure may be involved in the pathogenic capabilities of *N. perurans* [78] While the exact role of the PLO in pathogenesis of *N. perurans* remains unknown, genome and transcriptome analyses of the closely related *N. pemaquidensis* and its associated PLO detailed the interconnected relationship of both metabolisms [88]. For example, synthesis of the antioxidant trypanothione in the PLO is made possible using glutathione and spermidine synthesised by the host and the functionality of biosynthetic pathways such as heme or purine metabolism appear to be reliant on genes from both organisms [88].

Further to the aforementioned findings, species such as betaproteobacteria *Candidatus Branchiomonas cysticola* and the flavobacterium *Tenacibaculum maritimum* have been identified as contributors of CGD [8,54]. These pathogens can colonise gills between 12-and 16-weeks post-seawater transfer with *D. lepeophtherii* and *Candidatus B. cysticola* appearing most prevalent [20]. As causative agents of CGD are less characterised than AGD further investigations are required to evaluate the virulence potential of other pathogens.

Table 1. Microbial Interactions during Marine Gill Disease (associations and co-infections) and their pathogenicity potential.

Organism	Gill Disease	Location	Method of Analysis	Pathogenicity Potential
Amoebae				
N. perurans (only instances of coinfection with other gill diseases were included)	PGI [58]	Norway	Gills, heart and kidney of Atlantic salmon and rainbow trout diagnosed with PGI were examined. Smears made from gills were assessed microscopically and screened using RT-PCR for bacteria, *Ichthyobodo* spp., *Trichodina* spp. and *Neoparamoeba* spp.	Normally known as the causative agent in AGD. Co-isolation with other potential pathogens indicates multifactor causation of disease
	CGD [75]	Norway	Gills of Atlantic salmon were assessed through histological examination, following by qPCR analysis of gills sampled for Ca. *Piscichlamydia salmonis*, Ca. *Branchiomonas cysticola*, *Desmozoon lepeophtherii and N. perurans* from 22 geographically spread outbreaks.	
	CGD [54]	Norway	Gills from sea-farmed salmon with suspected GD underwent histopathological examination and in situ hybridisation (ISH) for *Ca B. cysticola*, *D. lepeoptherii* and SGPV. Single-plex PCR was used for the detection of *N. perurans*, *Ca B. cysticola*, *D. lepeoptherii* and Ca. *P. salmonis.*	
	GD [89]	Norway	During a cohort study, Atlantic salmon were sampled and assessed by gross gill scoring during the sea phase. Gills were assessed histologically and using qPCR analysis to screen for Ca. *B. cysticola,* SGPV, *D. lepeophtherii* and *N. perurans*	
N. pemaquidensis (7 isolations)	AGD [90]	Spain	Amoebae were isolated from the gills of turbot *Scophthalmus maximus L.* Trophozoites found in gill tissues and those cultured displayed the principal characteristics of *N. pemaquidensis*	Originally considered the causative agent of AGD [27] however, in challenge experiments, isolates of *N. pemaquidensis* obtained from AGD infected salmon failed to cause AGD [32,91] and only established a mild infection [92]. Furthermore, despite multiple occurrences of *N. pemaquidensis* being observed/isolated during AGD this species has been retrieved from the sediment of areas with no outbreak history [93].
	AGD—with or at risk of AGD [94]	Tasmania	Amoebae isolates were cultured from the gills of salmon, late in the infection of AGD and assessed morphologically using immunostaining of gill samples and observed growth characteristics of cloned cultures, consistent with *N. pemaquidensis*	
	AGD [95]	Tasmania	Amoebic isolates from Atlantic salmon gills were examined morphologically and characterised using PCR and sequencing (18s rRNA)	
	AGD [77]	Tasmania	Amoebic isolates from Atlantic salmon gills were examined morphologically and characterised using PCR and sequencing (SSU rRNA)	

Table 1. *Cont.*

Organism	Gill Disease	Location	Method of Analysis	Pathogenicity Potential
			Amoebae	
	AGD [91]	Tasmania	Amoebic isolates from Atlantic salmon gills were examined morphologically and characterised using PCR and sequencing (18s rRNA)	
	AGD—with or at risk of AGD [96]	Ireland	Gills of Atlantic salmon were examined morphologically and confirmed using *Neoparamoeba* spp.-specific immunofluorescent anti-body test (IFAT) and PCR of 18s rRNA gene using specific *N. pemaquidensis* primers	
	GD [92]	Norway	Amoebae isolated from salmon showing signs of GD, with a saithe from the farmed cage were cloned and sequenced using SSU rRNA	
N. branchiphila (1 isolation)	AGD [77]	Tasmania	Through the screening of 18 *Neoparamoeba* strains isolated from gills of Atlantic salmon, sediments and surrounding sea cages, isolates were characterised morphologically and sequenced (SSU rRNA).	Since N. branchiphila was discovered [76] it has been defined as the causative agent of infection of moribund sea urchins Diadema aff. antillarum in Tenerife, Canary Islands, Spain [97].
Neoparamoeba spp. (unidentified) (2 isolations)	PGD [66]	Norway	Detected through partial 18s sequencing of gills from Atlantic salmon infected with PGD	Co-infection and incidental presence of *Neoparamoeba* warrant further study to understand how infection is established
	GD [39]	Ireland	Gill samples of Atlantic salmon were assessed by histopathological examination and screened for bacteria, fresh gill scraping and smears were examined on-site using light microscopy	
P. eilhardi (2 isolations)	AGD [94]	Tasmania	Amoebae isolates were cultured from salmon gills, with clear signs of AGD and assessed morphologically using immunostaining and by observing growth characteristics of cloned cultures, where one of six *Paramoeba* spp. isolated was assumed to be *P. eilhardi*	Currently, the pathogenicity of *P. eilhardi* has yet to be investigated. The first official report of *P. eilhardi* being isolated from the gills of teleost fish was in 2019 [98]. Previously, Howard, 2001 proposed a retrieved isolate to be P. eilhardi however, this was not confirmed molecularly [94].
	AGD [98]	Tasmania	Amoeba isolates from Atlantic salmon gills, displaying clinical signs of AGD (score $\geq$ 3), were assessed morphology using light microscopy and TEM. Followed by sequencing (18S rRNA) and cytochrome oxidase subunit I (COI) gene—sequences were analysed phylogenetically	

Table 1. *Cont.*

Organism	Gill Disease	Location	Method of Analysis	Pathogenicity Potential
Amoebae				
Vannella spp. (4 isolations)	AGD [90,99]	Spain	Amoebae were isolated from turbot gills through culture and cloning then characterised using TEM	*Vannella* spp. are ubiquitous [84] however, are commonly present during disease, i.e., most commonly isolated during study of diseased rainbow trout in fresh water NGD [25] and also, have been seen in communities of epizoic gymnamoebae on gills of turbots where no gill abnormalities were observed but fish displayed slight behavioural changes indicative of suboptimal health [99].
	AGD—with or at risk of AGD [94]	Tasmania	Amoeba isolates from salmon gills, late in infection of AGD, were assessed morphologically using immunostaining, followed by observing growth characteristics of cloned cultures through microscopy, where *Vannella* spp. were the second most commonly isolated marine amoeba during the study	
	AGD [98]	Tasmania	Amoeba isolates from Atlantic salmon gills, displaying clinical signs of AGD (score $\geq$ 3), were assessed morphology using light microscopy and TEM. Followed by sequencing (18S rRNA) and cytochrome oxidase subunit I (COI) gene—sequences were analysed phylogenetically with *Vannella* having the greatest species diversity.	
	GD [92]	Norway	Amoebae were obtained from the lice *Lepeophtheirus salmonis*, attached to salmon with GD, the amoebae were cloned and identified using sequencing of the partial small subunit (SSU) rRNA gene	
Platyamoeba spp. (4 isolations)	AGD [26]	Spain	Amoebae were isolated from the gills of moribund farmed turbot and identified using light and electron microscopy	Commonly associated with AGD [26,90,94,99]. Currently, *Platyamoeba* spp. are not considered pathogenic to Atlantic salmon due to findings from a challenge trial (*Platyamoeba* spp. isolated from the gills of Atlantic salmon in Ireland were not associated with gill lesions and did not elicit disease [74]). However, authors noted how the virulence of the strain may have decreased during cryopreservation and culturing.
	AGD [90,99]	Spain	Amoebae were isolated from the gills of turbot through culture and cloning, then characterised using TEM	
	AGD—with or at risk of AGD [94]	Tasmania	Amoeba cultured from salmon gills, with clear signs of AGD were present and assessed morphologically using immunostaining of gill samples and through observing the growth characteristics of cloned cultures and/or microscopy, where *Platyamoeba* were one of two most commonly isolated marine amoebae during the study	
	AGD—with or at risk of AGD [96]	Ireland	Amoebae isolates were cultured from the gills of Atlantic salmon smolts and identified morphologically using light, fluorescence, and transmission electron microscopy	

Table 1. *Cont.*

Organism	Gill Disease	Location	Method of Analysis	Pathogenicity Potential
			Amoebae	
Vexillifera spp. (3 isolations)	AGD—with or at risk of [94]	Tasmania	Amoeba isolates were cultured from the gills of salmon, late in infection when signs of AGD were present and assessed morphologically using immunostaining of gill samples and through observing the growth characteristics of cloned cultures and/or microscopy	Certain members of genus *Vexillifera* are understood to induce infections (*V. bacillipedes*, the causative agent of seasonal epizootics of systemic amoebiasis in hatchery-reared rainbow trout in Italy [100]) but as disease caused by this species are fresh water limited [94] and *Vexillifera* spp. have been isolated from various other asymptomatic fish (gills and organs) [101] there are no current indications of pathogenicity during GD.
	AGD—with or at risk of AGD [96]	Ireland	Amoebae isolates cultured from gills of Atlantic salmon smolts were identified morphologically using light, fluorescence and transmission electron microscopy	
	AGD [98]	Tasmania	Amoeba isolates from Atlantic salmon gills, displaying clinical signs of AGD (score $\geq$ 3), were assessed morphology using light microscopy and TEM. Followed by sequencing (18S rRNA) and cytochrome oxidase subunit I (COI) gene—sequences were analysed phylogenetically	
Flabellula spp. (3 isolations)	AGD [90,99]	Spain	Amoebae isolated from turbot gills through culture and cloning, then characterised using TEM	*F. calkinsi* or *F. citata* through morphology anlaysis [94,96,99]. Their potential as pathogens has been studied further.
	AGD—with or at risk of AGD [94]	Tasmania	Amoebae isolates were cultured from salmon gills, with clear signs of AGD and assessed morphologically using immunostaining and by observing growth characteristics of cloned cultures microscopically	
	AGD—with or at risk of AGD [96]	Ireland	Amoebae isolates cultured from gills of Atlantic salmon smolts were identified morphologically using light, fluorescence and transmission electron microscopy	
Nolandella spp. (2 isolations)	AGD—with or at risk of AGD [96]	Ireland	Amoebae isolates were cultured from the gills of Atlantic salmon smolts and identified morphologically using light, fluorescence and transmission electron microscopy	*Nolandella* strains are able to colonise the gills of marine teleost [98,102] however, during a challenge trial, cultured *Nolandella* spp. did not induce AGD and did not influence the severity of AGD during the early stages of development [103].
	AGD [98]	Tasmania	Amoeba isolates cultured from Atlantic salmon gills displaying clinical signs of AGD (score $\geq$ 3), were assessed morphology using light microscopy and TEM, then sequenced (18S rRNA) and cytochrome oxidase subunit I (COI) gene—sequences were analysed phylogenetically	

Table 1. *Cont.*

Organism	Gill Disease	Location	Method of Analysis	Pathogenicity Potential
			Amoebae	
Pseudoparamoeba spp. (1 isolation)	AGD [98]	Tasmania	Amoeba isolates cultured from the gills of Atlantic salmon, displaying clinical signs of AGD (score $\geq$ 3), were assessed morphology using light microscopy and TEM then molecularly by sequencing of the 18S ribosomal RNA (18S rRNA) gene and cytochrome oxidase subunit I (COI) gene sequences were analysed phylogenetically	*Pseudoparamoeba* sp. being isolated from the gills of Atlantic salmon was first documented in 2019 [98] and subsequently investigated. *Pseudoparamoeba* did not induce AGD or influence severity [103]. As these amoebae are rare in the environment [104] they are not presumed to play a role in GD.
Acanthamoeba spp. (1 isolation)	AGD—with or at risk of AGD [94]	Tasmania	Amoeba isolates were cultured from salmon gills, with clear signs of AGD were assessed morphologically using immunostaining and through observing the growth characteristics of cloned cultures and/or microscopy	Various *Acanthamoeba* spp. are pathogenic to humans [105] however, due to low isolation rates and failure to grow on seawater agar their potential as fish pathogens has not been explored [94].
Mayorella spp. (1 isolation)	AGD—with or at risk of AGD [96]	Ireland	Amoebae isolates were cultured from the gills of Atlantic salmon smolts and identified morphologically using light, fluorescence, and TEM.	No current direct pathogenic potential noted however, some species have been observed to host parasitic fungi [106,107].
Tetramitus spp. (1 isolation)	GD [92]	Norway	Amoebae isolated from the gills of farmed salmon with GD and identified using sequencing of the partial small subunit (SSU) rRNA gene	Deemed as a non-virulent amoeba [108] and unable to cause lasting infection on salmon gills [92].
			Bacteria present in Epitheliocystis	
Candidatus Branchiomonas cysticola (5 isolations)	PGI [62]	Norway	Atlantic salmon gills with clinical signs of PGI were assessed by histological examination and TEM, then molecular methods were used to identify the bacterium responsible for epitheliocysts, fluorescence ISH confirmed its localisation within cysts	They transfer horizontally with infections occurring in naïve fish in high prevalence [109]. Ca. *B. cysticola* has been associated with necrosis and inflammation [54] and also, observed in small foci within areas of inflammation, without the presence of epitheliocysts [89].
	PGI [110]	Norway and Ireland	Bacterium was quantified using a specific and sensitive RT-PCR assay in Atlantic salmon gills over a 7-year survey and over 17 distinct locations, fluorescence ISH confirmed its localisation within cysts	
	CGD [75]	Norway	Atlantic salmon gills were assessed through histological examination, following qPCR analysis for Ca. *P. salmonis*, Ca. *B. cysticola*, *D. lepeophtherii* and *N. perurans* from 22 geographically spread outbreaks	

Table 1. *Cont.*

Organism	Gill Disease	Location	Method of Analysis	Pathogenicity Potential
			Amoebae	
	AGD [20]	Ireland	Atlantic salmon gills with AGD were assessed using a histopathology score, and RT-PCR was used to determine the presence and sequential infection patterns of pathogens on samples collected from stocking until harvest	
	CGD [54]	Norway	Sea-farmed salmon gills with suspected GD were investigated using histopathological examination and ISH for *Ca B. cysticola, D. lepeoptherii* and SGPV, single-plex PCR was used for the detection of *N. perurans*, *Ca B. cysticola*, *D. lepeoptherii* and Ca. *P. salmonis*.	
	GD [89]	Norway	Atlantic salmon were sampled, and gross gill scoring was performed in the sea phase and were assessed histologically and using qPCR to screen *for* Ca. *Branchiomonas cysticola*, salmon gill poxvirus, *Desmozoon lepeophtherii* and *N. perurans*	
Candidatus Piscichlamydia salmonis (6 isolations)	PGD [66]	Norway	Detected through qPCR and 16s sequencing from the gills of Atlantic salmon infected with PGD	Despite Ca. *P. salmonis* being commonly isolated in the presence of cysts and infecting naïve fish at low prevalence during a challenge trial, these bacteria are not associated with observed cysts [62]. Other bacteria of order *Chlamydia* are also present in the freshwater stage of salmon gill infections (*Ca. Clavochlamydia salmonicola*) [111] which may contribute to compromised health in Atlantic Salmon before sea transfer.
	PGI [65]	Norway	The gill-associated bacterial community of Atlantic salmon suffering PGI (diagnosed by histology) was compared with clinically healthy fish using RT-PCR Reaction-Denaturing Gradient Gel Electrophoresis	
	PGI [112]	Norway	Atlantic salmon gills were analysed by histological examination and by RT- PCR using specific probes (‘*Ca. P. salmonis*’ 16S rRNA gene assay)	
	PGI [58]	Norway	The gills, heart and kidney of Atlantic salmon and rainbow trout diagnosed with PGI were examined, the smears taken were visually assessed microscopically and screened using RT-PCR for bacteria; *Ichthyobodo* spp., *Trichodina* spp. and *Neoparamoeba* spp.	
	PGI [62]	Norway	Atlantic salmon gills with clinical signs of PGI were assessed by histological examination and TEM, then molecular methods were used to identify the bacterium responsible for epitheliocysts, this bacterium were present but not responsible for cysts	
	CGD [75]	Norway	Atlantic salmon gills were assessed through histological examination, following qPCR analysis of gills sampled for Ca. *P. salmonis*, Ca. *B. cysticola, D. lepeophtherii* and *N. perurans* from 22 geographically spread outbreaks	

Table 1. *Cont.*

Organism	Gill Disease	Location	Method of Analysis	Pathogenicity Potential
			Amoebae	
	CGD [54]	Norway	Gills from sea-farmed salmon with suspected GD were investigated using histopathological examination and ISH for *Ca B. cysticola*, *D. lepeoptherii* and SGPV. Single-plex PCR was used for the detection of *N. perurans*, *Ca B. cysticola*, *D. lepeoptherii* and Ca. *P. salmonis*	
Candidatus Syngnamydia salmonis (1 isolation)	GD [63]	Norway	Salmon with GD, from three separate seawater farms, underwent RNA extraction and qPCR. Histology examination, TEM and fluorescence ISH were used to identify bacterium responsible for epitheliocysts	
Undetermined Epitheliocystis (2 isolations)	GD [39]	Ireland	Atlantic salmon gills were assessed using histopathological examination and screened for bacteria, with fresh gill scrapes and smears were examined on-site using light microscopy	
	PGI [55]	Norway	The gills of diseased fish from 3 seawater farms were sampled, pathological changes were described and macroscopically characterised, the aetiological significance of ASPV was studied by immunofluorescent staining of cryosections and by immunohistochemistry on sections of formalin-fixed and paraffin-embedded tissue	
			Bacteria present in Tenacibaculosis	
Tenacibaculum spp. (uncharacterised) (2 isolations)	PGI [65]	Norway	The gill-associated bacterial community of Atlantic salmon suffering from PGI (diagnosed by histology) was compared with clinically healthy fish using RT-PCR Reaction-Denaturing Gradient Gel Electrophoresis	Causative agent of Tenacibaculosis. They may contribute to AGD pathogenesis but the presence of *T. maritimum* could not be statistically associated with increased gill scores [113]. The presence of *T. maritimum* significantly correlated with temperature showing distinct seasonality [20] (a common risk factor of AGD). *T. dicentrarchi* may significantly contribute to AGD as its population was considerably higher in diseased tissue than unaffected tissue [8]. The authors highlight a significance due to the role of extracellular products in infection that degrade host epithelial cells [64]. *T. maritinum* was also isolated from jellyfish samples [114].
	GD [39]	Ireland	Atlantic salmon gill tissues were assessed by histopathological examination and screened for bacteria, fresh gill scrapes and smears were examined on-site using light microscopy	
Tenacibaculum maritimum (1 isolation)	AGD [20]	Ireland	Atlantic salmon gills were assessed during AGD using a histopathology score, with RT-PCR being used to determine the presence and sequential infection patterns of pathogens on gill samples collected from stocking until harvest	
Tenacibaculum dicentrarchi (1 isolation)	AGD [8]	Tasmania	Bacteria isolated from the gills of Atlantic salmon, identified using 16s rRNA sequencing and levels investigated using qPCR	

Table 1. *Cont.*

Organism	Gill Disease	Location	Method of Analysis	Pathogenicity Potential
Amoebae				
Other bacteria isolated from gills				
Vibrio spp. (2 isolations) (family Vibrionaceae, phylum Pseudomonadota) (*Vibrio tapetis* and *Vibrio anguillarum* [115])	AGD [115]	Korea	Isolated from gray mullet and identified by 16S rRNA gene sequencing during an investigation of mortalities caused by *N. perurans*, affected species (black seabream, rock bream and gray mullet) added as new hosts for *N.perurans* infection	*Vibrio* spp. are detrimental pathogens in aquaculture with species infecting a wide marine host-range [83,116]. From the isolated species, *V. anguillarum* causes Vibriosis [117] and *Vibrio tapetis* is the causative agent of Brown Ring Disease seen in cultured Manila clam [118]. Also found in *N. perurans* and therefore could contribute to pathogenicity
Flavobacterium spp. (2 isolations) (family Flavobacteriaceae, phylum Bacteroidetes) *Flavobacterium psychrophilum* [58]	PGI [65]	Norway	The gill-associated bacterial community in Atlantic salmon suffering from PGI (diagnosed by histological examination) was compared with that of clinically healthy fish by Reverse Transcriptase Polymerase Chain Reaction-Denaturing Gradient Gel Electrophoresis	Flavobacteria are common pathogens during the freshwater phase of salmonoid aquaculture [80]. From the isolated species, *F. psychrophilum* are highly pathogenic, causing bacterial cold water disease [44]. For this reason, they have been considered to play a role in PGD [66].
	PGI [58]	Norway	The gills, heart and kidney of Atlantic salmon and rainbow trout diagnosed with PGI were examined, the smears made from gills were visually assessed by microscopy and screened using qPCR assays for bacteria, *Ichthyobodo* spp., *Trichodina* spp. and *Neoparamoeba* spp.	
Psychroserpens spp. (1 isolation) (family Flavobacteriaceae, phylum Bacteroidetes)	AGD [80]	Tasmania	Bacteria isolated from the gills of Atlantic Salmon infected with AGD (infected in the laboratory or obtained from commercial sea cages) and identified using bacteria-specific 16S rRNA gene primers	*Psychroserpens* spp. (family Flavobacteriaceae) are from the same family as detrimental salmonoid pathogens and the geographical distribution of these pathogens is strongly defined by water salinity [80] (a common risk factor in AGD).
Pseudomonas anguilliseptica	AGD [115]	Korea	Isolated from rock bream and identified by 16S rRNA gene sequencing, during an investigation of mortalities caused by *N. perurans*.	*P. anguilliseptica* is described to cause disease in fish farms in Korea [115,119].
Staphylococcus spp.	AGD [120]	Tasmania	Bacteria isolated and identified using 16S rRNA gene sequencing from 2 of 2 groups of Atlantic salmon with AGD (AGD positive farm and from an experimental AGD tank)	As well as being human pathogens [121,122], several species are pathogenic to various teleosts, e.g., *S. epidermidis* [123,124] and *S. xylosus* [125,126].

Table 1. *Cont.*

Organism	Gill Disease	Location	Method of Analysis	Pathogenicity Potential
			Amoebae	
Winogradskyella spp. (1 isolation) (family Flavobacteriaceae, phylum Bacteroidetes) (1 isolation)	AGD [120]	Tasmania	Bacteria isolated and identified using 16S rRNA gene sequencing from 2 of 2 groups of Atlantic salmon with AGD (AGD positive farm and from an experimental AGD tank)	*Winogradskyella* spp. are not known fish pathogens, but were found in abundance on fish gills with AGD [120] and in an exposure trial during AGD [81]. Similarly, *Winogradskyella* spp. were correlated with bleaching disease in red macroalgae, along with *Vibrio* spp., were deemed as candidate opportunistic pathogens [127].
Photobacterium spp. (family Vibrionaceae, phylum Pseudomonadota)	PGI [65]	Norway	The gill-associated bacterial community in Atlantic salmon suffering PGI (diagnosed by histology) was compared with that of clinically healthy fish by RT-PCR -Denaturing Gradient Gel Electrophoresis	Pathogenicity of multiple species in both fish and humans [128,129]. E.g., in fish, *P. damselae* Ssp. *piscicida* causes photobacteriosis [130] (formerly pasteurellosis [131]) and in humans the subspecies *damselae* causes necrotizing fasciitis [132].
Shewanella spp. (family Shewanellaceae, Phylum Pseudomonadota)	PGI [65]	Norway	The gill-associated bacterial community in Atlantic salmon suffering PGI (diagnosed by histology) was compared with that of clinically healthy fish by RT-PCR-Denaturing Gradient Gel Electrophoresis	Marine pathogens capable of causing disease in humans. *Shewanella* algae causes ulcer disease in fish [133] and can cause ulcers in humans [134]. Other members parasitic to fish [135] are also important fish spoilage organisms [136].
Aliivibrio spp. (family Vibrionaceae, phylum Pseudomonadota) Previously *Vibrio*, classified in 2007 [137]	PGI [65]	Norway	The gill-associated bacterial community in Atlantic salmon suffering PGI (diagnosed by histology) was compared with that of clinically healthy fish by RT-PCR-Denaturing Gradient Gel Electrophoresis	The pathogenic member of this genus is *A. salmonicida*, causing cold-water vibriosis (primarily affects farmed Atlantic salmon) [138]. *A. wodanis*, is commonly isolated during winter-ulcer disease along with the causative agent *Moritella viscosa* [139,140].
			Obligate parasites	
Desmozoon lepeophtherii syn. *Paranucleospora theridion* (7 isolations)	PGI [141]	Norway	N/A	*Paranucleospora theridion* (syn. Desmozoon lepeophtheirii) are parasitic to both salmon and salmon lice. Two spore types are produced in salmon, one in the cytoplasm of phagocyte or epidermal cells of and one in the nuclei or epidermal cells [142]. A third spore is produced in salmon louse in several different cell types [142]. Parasite densities are higher in autumn [51].
	PGI [112]	Norway	Atlantic salmon gills analysed by histological examination and qPCR	
	PGI [58]	Norway	Atlantic salmon and rainbow trout gills, heart and kidney were examined microscopically before using qPCR assays for bacteria, *Ichthyobodo* spp., *Trichodina* spp. and *Neoparamoeba* spp., DNA from tissues obtained the partial SSU rDNA sequence of *Desmozoon lepeophtherii* syn. *Paranucleospora theridion*	

Table 1. *Cont.*

Organism	Gill Disease	Location	Method of Analysis	Pathogenicity Potential
			Amoebae	
	PGI [143]	Scotland	Atlantic salmon gills assessed using light microscopy, staining and TEM, where *Desmozoon lepeophtherii* was identified using a Gram Twort method	
	AGD [20]	Ireland	Atlantic salmon gills assessed using histopathology and changing water temperatures. RT- PCR determined the presence and sequential infection patterns of pathogens on gill samples collected from stocking until harvest	
	CGD [75]	Norway	Atlantic salmon gills assessed using histopathology, followed by qPCR analysis for Ca. *P. salmonis*, Ca. *B. cysticola*, *D. lepeophtherii* and *N. perurans* from 22 geographically spread outbreaks	
	CGD [54]	Norway	Gills from sea-farmed salmon with suspected GD were investigated using histopathology and ISH for *Ca B. cysticola*, *D. lepeoptherii* and SGPV. Single-plex PCR was used for the detection of *N. perurans*, *Ca B. cysticola*, *D. lepeoptherii* and Ca. *P. salmonis*	
	GD [89]	Norway	Atlantic salmon were assessed by gross gill scoring during the sea phase, then assessed histologically and used qPCR analysis to screen for *Ca B. cysticola*, salmon gill poxvirus, *Desmozoon lepeophtherii* and *Neoparamoeba perurans*	
Ichthyobodo spp. (3 isolations)	PGI [55]	Norway	The gills of diseased fish from 3 seawater farms were sampled, pathological changes were described and macroscopically characterised, the aetiological significance of ASPV was studied by immunofluorescent staining of cryosections and by immunohistochemistry on sections of formalin-fixed and paraffin-embedded tissue	Known to cause Ichthybodosis, causing cellular destruction
	GD [39]	Ireland	Atlantic salmon gills assessed histopathologically and screened for bacteria, fresh gill scrapes and smears were examined on-site using light microscopy	
	PGI [58]	Norway	The gills, heart and kidney of Atlantic salmon and rainbow trout diagnosed with PGI were visually assessed by microscopy and using RT-PCR assays for bacteria, *Ichthyobodo* spp., *Trichodina* spp. and *Neoparamoeba* spp.	

Table 1. *Cont.*

Organism	Gill Disease	Location	Method of Analysis	Pathogenicity Potential
			Amoebae	
Trichodina spp. (3 isolations)	PGI [55]	Norway	The gills of diseased fish from 3 seawater farms were sampled. Pathological changes were described and macroscopically characterised, the aetiological significance of ASPV was studied by immunofluorescent staining of cryosections and by immunohistochemistry on sections of formalin-fixed and paraffin-embedded tissue	Ectoparasites in aquaculture [144,145] with a wide host range [146–149].
	GD [39]	Ireland	Atlantic salmon gills assessed histopathologically and screened for bacteria, fresh gill scrapes and smears examined on-site using light microscopy	
	PGI [58]	Norway	The gills, heart and kidney of Atlantic salmon and rainbow trout with PGI were visually assessedmicroscopically, and screened using qPCR assays for bacteria, *Ichthyobodo* spp., *Trichodina* spp. and *Neoparamoeba* spp.	
			Viruses	
Salmon gill poxvirus (SGPV) (5 isolations)	PGD [66]	Norway	Atlantic salmon gills infected with PGD were assessed histologically and with TEM. Followed by RT-PCR, and PCR to screen for Candidatus Piscichlamydia salmonis and Atlantic salmon paramyxovirus (ASPV) (fish negative for ASPV)	Poxviruses can infect non-farmed fish, such as the ayu [67]. SGPV was the only pathogen found in the freshwater farm prior to PGD infection [66] and considered a primary pathogen in CGD [150]. Furthermore, instances of reinfection of SGPV have been noted (suggesting no immunity after first infection) [89].
	CGD [75]	Norway	Atlantic salmon gills assessed through histological examination, following qPCR analysis for Ca. *P. salmonis*, Ca. *B. cysticola*, *D. lepeophtherii* and *N. perurans* from 22 geographically spread outbreaks	
	AGD [20]	Ireland	Atlantic salmon gills were assessed during AGD using gill histopathology score, RT-PCR was used to determine the presence and sequential infection patterns of pathogens on gill samples collected from stocking until harvest	
	CGD [54]	Norway	Sea-farmed salmon with suspected GD underwent histopathological examination and ISH for *Ca B. cysticola*, *D. lepeoptherii* and SGPV. Single-plex PCR was used for the detection of *N. perurans*, *Ca B. cysticola*, *D. lepeoptherii* and Ca. *P. salmonis*	

Table 1. *Cont.*

Organism	Gill Disease	Location	Method of Analysis	Pathogenicity Potential
			Amoebae	
	GD [89]	Norway	Atlantic salmon were sampled and assessed by gross gill scoring during the sea phase, gills were assessed histologically and using qPCR analysis to screen for *Ca B. cysticola*, salmon gill poxvirus, *Desmozoon lepeophtherii* and *N. perurans*	
Atlantic salmon paramyxovirus (ASPV) (3 isolations)	GD [151]	Norway	The virus was isolated by suspension of gill tissues, cell cultures were assessed using electron microscopy and the viral peptides using gel electrophoresis	Other paramyxovirus-like agents have been observed or isolated from rainbow trout in Germany, from seabream in Japan associated with epithelial necrosis, from turbot in Spain associated with erythrocytic inclusion bodies and buccal/opercular haemorrhaging and from koi and common carp associated with gill necrosis in the European Union [152].
	Epitheliocystis [59]	Norway	Presence of virus was determined using a set of internal gene-specific PCR primers used on DNA from ASPV-infected cells and tissues	
	PGI [55]	Norway	A rabbit hyperimmune serum against ASPV was produced, characterized, and used to detect viral antigen in the gills of Atlantic salmon, by an indirect immunofluorescence (IIF) test on cryosections and immunohistochemistry (IHC) on sections of formalin-fixed and paraffin-embedded tissue	
			Cnidarians	
Hydrozoans (1 isolation)	GD [39]	Ireland	Gill samples of Atlantic salmon were assessed by histopathological examination and screened for bacteria, fresh gill scrapes and smears were examined on-site using light microscopy	Cnidarians are commonly associated with GD [153,154] and have been the causative agent of fish kills in Ireland [155] and associated with an increase in gill pathology and mortality in Scotland [156]. These species cause irritation to the gills (i.e., stinging) [157] as well as fouling (limiting water quality), shown experimentally to cause pathological changes on gills [38,158]. Furthermore, the myxozoan *Henneguya ictaluri* within the phylum Cnidarians is responsible for fresh water PGD in catfish [71,159].

3. Climate Change Can Impact Microbial Populations and Interactions

Climate change is a growing global concern and as with many industries, is expected to have a significant impact on aquaculture and marine life's susceptibility to diseases [17,160]. Although it impacts a variety of aquatic factors such as sea level, turbidity through extreme weather conditions, salinity, pH, temperature and nutrient loading, little is understood about the impact on ecosystems and the microbial communities [35,161]. This is key with regard to evaluating multitrophic levels and the ability of key species to control or contribute to the prevalence of diseases such as AGD and CGD [162].

Further still, research is yet to fully elucidate the impact of anthropogenic influences such as metal and organic pollutants released into the environment on microbial communities and the subsequent effect on fish health [163] and susceptibility to GD. There have however been numerous studies on the impact of temperature change [12]. For example, there has been a noticeable effect of temperature on salmon growth rates, which has been linked to metabolic depression [10]. Salmon grown in higher temperatures, above 15 °C compared to 13 °C, resulted in a chronic stress response [10]. Conversely, in Tasmania, salmon showed preference to temperatures between 16.5–17.5 °C [164], whereas other work witnessed growth in temperatures as high as 22 °C [165]. It is likely that there is a thermal tolerance where the impact on the host depends on the environmental conditions which they are acclimatised to and incremental changes to said environment might cause additional stress and susceptibility to disease. This phenomenon was further investigated through the evaluation of acclimatisation and metabolic requirements during the acquisition of AGD, which determined a minimal impact of acclimation on metabolism, suggesting the temperature-disease interaction may be more complicated than currently thought [166]. It has been demonstrated that temperature is a significant factor in maintaining regular fish immune functions. High temperatures have been shown to cause upregulation of cytokine genes and increases in IgM at 25 °C in rainbow trout (vaccinated with *Yersinia ruckeri* serotype O1) [167], as well as an increase in the number of neutrophils and lower levels of Ig+ cells in the blood of Atlantic salmon at 18 °C [168]. Problematically, this again does not demonstrate the effect of a habitant's environment changing, i.e., they could be used to higher or lower temperatures, but how does an incremental increase impact their susceptibility to disease.

They have however shown that warmer temperatures increase amoebic reproduction [33] and elevated stress levels in salmon [14] resulting in a supressed immune system [15]. A study in Scotland demonstrated an increase in AGD severity in Atlantic salmon at 15 °C compared to 10 °C through the analysis of histopathology and *N. perurans* (described as *Paramoeba* in this study) load on the gills [14]. Interestingly there was no change in cortisol levels but an increase in glucose and lactate levels at both temperatures, suggesting other environmental changes could be the resulting cause. With regard to CGD, recent work by Jones and Price (2022) observed a statistically significant relationship between elevated seawater temperatures and elevated gill scores of farmed Atlantic salmon, results also highlighted the direct relationship between salinity and gill score however, only in the presence of *N. perurans* [169]. This work reiterates the influence of temperature on the severity of CGD and the importance of *N. perurans* infection in the development of CGD.

The long-term impact of climate change could result in the emergence of resistance in both host and pathogen through genetic adaptions that may only be evident through temporal analysis. These adaptations could impact virulence [35] and potentially new emerging infectious diseases may be discovered. Benedicenti and colleagues (2018) explored this and were able to demonstrate that this might have a potential role in virulence of *N. perurans* by altering the bacterial communities associated with AGD. They also showed that temperature had a significant effect on *Pseudomonas* growth derived from amoebae cultures, and 30 of the most prevalent bacteria genera—where the growth changes corresponded with the amoebae growth—highlighting an associated bond between amoebae and bacteria, influenced by temperature [33].

4. Conclusions and Research Recommendations

GD is a tremendous challenge in the aquaculture industry and many microorganisms contribute directly to GD or have been isolated during GD cases. The diverse range of terms used in literature to describe similar outbreaks and pathologies have made it challenging to compare cases and draw conclusions [4]. Additionally, the presence of multiple pathogens in GD has made investigating host-pathogen relationships and co-infections convoluted. Although presumed primary and secondary pathogens have been recorded for GD, the challenge remains to successfully culture main offenders (SGPV, *D. lepeophtherii* and Ca. *Branchiomonas cysticola)* in vivo [3]. Moreover, the culturing of *N. perurans* is confounded by bacterial load, which hints at the importance of potential bacterial endosymbionts, and this could be the case. *N. perurans* are involved in complex intracellular and extracellular interactions which should be investigated thoroughly, with aims to identify potential symbionts that may aid in survival and virulence in AGD, which is an ever-increasing global threat in aquaculture [78].

When investigating potential pathogenicity symbionts of GD causing pathogens, the role of autochthonous organisms present in the microbiome should not be overlooked, as there is the potential for organisms to become infectious under specific circumstances, i.e., infections are dose-dependent [20], where Steinum et al., 2010 detected *D. lepeophtherii* in a >30 times higher microsporidian load in fish with PGI compared to unaffected fish [112] and Mitchell et al., 2013 found Ca. *B. cisticola* bacterial loads to coincide with pathological changes in the gills [110]. The significance of the microbiome in teleost aquaculture should also be investigated, in particular, Atlantic salmon, as their susceptibility to GD is well documented but less known are the reasons why they are susceptible. The fact that these teleosts are farmed in both fresh and marine environments may be significant as infectious agents of marine GD (i.e., SGPVD, Epitheliocysts and *Ichthyobodo* species) are also present in freshwater salmonoid aquaculture. Furthermore, the management and treatment of salmon health may have indirect correlation to CGD outbreaks [12] as it is known that cleaner fish may spread pathogens and also, hydrogen peroxide bathing may compromise gill surface and leave it vulnerable to infection; with this in mind, studies investigating CGD after treatments may address these concerns [4].

The role of environmental factors contributing to GD warrants further research (e.g., temperatures, salinity, pH, as well as the microbial environment), as does the impact of these factors on the associated organisms of GD as well as the relationship the described amoebae have with the natural environment, where knowledge on natural distribution and reservoirs of transmission (particularly *N. perurans* [12]) are limited. These factors should be examined to aid mitigation strategies.

As the complexity of this disease may prove challenging to provide a specific treatment, mitigation may be the method of alleviating this disease and the pressures associated. Research should also focus on vaccination development for AGD as current studies cannot be truly compared due to differences in temperature, challenge concentration and source of the amoebae and host. To aid this challenge, Hudson and Nowak, 2021 suggest utilising realistic concentrations of amoebae in challenge models, using relevant endpoints to aquaculture industry (e.g., sample time to reinfection or gross gill score) and multiple endpoints to provide more knowledge on the disease [170]. This may also be a viable option for the treatment of CGD, if specific bacteria/viruses are confirmed to promote disease [4].

Overall, the prevention, diagnosis and mitigation strategies used in GD are hindered by a lack of standardised methods (especially AGD, where recent updates to the gill scoring system now encompass multifactorial pathologies [171]). These should aim to develop clear and defined characteristics of disease, along with stage of infection and should also clear up the mixed aetiologies around complex gill disease, this will ultimately improve recording of infection and enhance the literature and data surrounding GD which could advance disease control/treatments.

Future research should aim to discover and validate symbiotic relationships between bacteria and amoebae to uncover potential indicator organisms of AGD outbreaks and CGD,

with aims to identify targets for disease control/treatment. Specifically, the intracellular kinetoplast symbiont which *N. perurans* possess [172]. Even though the PLO was noted to possess SL RNA genes which deviate considerably from other kinetoplastids [86], this intracellular structure might be important in cellular survival and as such, presents an interesting therapeutic target. Significant research has been undertaken to tackle kinetoplast parasites of humans such as *Trypanosoma* spp. [173] and *Leishmania* spp. and repurposing strategies used to exploit these organisms may offer an effective approach to tackling AGD.

In conclusion there is a wealth of unknown variables in relation to GD, whether that be in the form of AGD, CGD, or other previously mentioned forms. Evidence suggests it is unlikely to have one cause, and we need to investigate a variety of multifactorial parameters. This includes recognising the current and futuristic impact of climate change, on the host-predator dynamic, the microbiome and pathobiome, as well as how changes in the physicochemical and geochemical parameters impact all of these.

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