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养殖水环境中抗生素对鱼类肠道菌群结构、功能和抗性组的影响研究进展

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摘要: 当前,抗生素类药物被广泛应用于水产养殖业,且在水环境中频繁检出多种类型的抗生素。抗生素和抗生素抗性基因(antibiotic resistance genes, ARGs)是多重耐药菌甚至“超级细菌”产生的源头,抗生素被列为一类新兴的有机污染物,对环境中生物的潜在不利影响已引起广泛关注。鱼类的肠道菌群会通过自身的细胞组分或代谢产物,影响鱼类的营养代谢、系统发育和免疫调节等生理过程。鱼类肠道菌群保持健康平衡状态能保障鱼体健康,水产养殖环境中残留的抗生素会对鱼类肠道菌群造成严重影响,相关研究已经展开。本文总结归纳了近年来部分国内外养殖水环境中抗生素的污染状况。基于目前的研究成果重点综述了抗生素对鱼类肠道菌群结构、功能和抗性组的影响,为抗生素的毒理学评价提供总结和新的研究思路,为进一步开展抗生素环境风险评估及制定污染防控阻断策略等研究提供参考。

关键词: 抗生素;鱼类;健康风险;肠道菌群;抗性组
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Research Progress on Effects of Antibiotics in Aquaculture Water Environment on Structure, Function and Resistome of Fish Intestinal Microbiota

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Abstract: Antibiotics are currently utilized extensively in the aquaculture industry, and multiple antibiotic types are frequently identified in water environments. Antibiotics and antibiotic resistance genes (ARGs) are the sources of multidrug-resistant bacteria and “superbug”. Antibiotics have been categorized as an emerging organic pollutant, and their potential detrimental effects on organisms in the environment have attracted widespread attention. Fish intestinal microbiota can affect nutrition metabolism, system development, and immune regulation of physiological processes via its own cell components or metabolites. And fish with a healthy intestinal microbiota balance can protect fish body health; aquaculture's residual antibiotics in the environment will have a serious influence on fish intestinal microbiota, and research in this area has begun. This paper summarizes the current status of an-

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tibiotic pollution in aquaculture water environments at home and abroad in recent years. In addition, the effects of antibiotics on the structure, function, and resistance groups of fish intestinal microbiota were mainly reviewed, providing a summary and new research ideas for toxicological evaluation of antibiotics as well as a reference for future research on environmental risk assessment of antibiotics and the development of pollution prevention and control strategies.

Keywords: antibiotics; fish; health risk; intestinal microbiota; resistome

抗生素最初是用来治疗动物疾病,后来逐渐作为饲料添加剂、预防剂和生长促进剂,使用量和使用频次逐年上升[1-2]。据报道全球 73% 的水产养殖国家使用土霉素、磺胺嘧啶和氟苯尼考,55% 的国家在水产养殖中使用磺胺二甲氧嘧啶、红霉素、阿莫西林和恩诺沙星[3]。抗生素的使用会直接影响鱼体肠道菌群的稳定。鱼类肠道菌群在营养合成和代谢、肠道上皮发育以及免疫系统调节等方面发挥重要作用[4],肠道菌群紊乱则会进一步影响鱼体的生理功能。

此外,抗生素的生物利用率仅为 10% ~30%,致使大量抗生素以母体及其代谢物形式进入养殖水环境中[5]。同时,抗生素持续不断地输入造成在水环境中形成一种假持久性现象[6]。一些抗生素在亚致死剂量下能显著促进质粒介导的抗生素抗性基因(antibiotic resistance genes, ARGs)水平转移,比如常见的氟诺喹酮类药物可通过接合转移促进 ARGs 在不同细菌之间进行传播[7-8]。一旦细菌获得 ARGs,即使在选择压力消失后,它们也可以在环境中长期存在[9]。ARGs 在生态环境中的传播、迁移和扩散已成为影响全球公共卫生安全的重要问题[10]。2021 年 9 月,*Nature* 发表的综述文章指出在水产养殖业中超过 50% 的水产养殖环境和养殖生物存在耐药性问题[11]。研究发现,已有 90% 以上的水生细菌能够抵抗超过 1 种抗生素,大约 20% 的细菌能抵抗 5 种甚至更多抗生素[12]。根据世界卫生组织(2019)[13]的报告,如果不采取行动,到 2050 年抗生素耐药性每年将导致 1 000 万人死亡,并使全球经济陷入危机。然而,抗生素的使用和 ARGs 的产生和传播之间的关联机制仍未明确。因此,本文总结归纳了养殖水环境中的抗生素残留现状,着重以抗生素对鱼类肠道菌群结构、功能及抗性组的影响为主线进行总结讨论,以期为环境中抗生素对鱼类肠道健康和 ARGs 传播的影响研究提供参考,也为在水产养殖中合理使用抗生素提供借鉴。

1　抗生素在养殖水环境中的残留现状(Status of antibiotic residues in aquaculture water environment)

1.1　养殖水环境中抗生素残留的原因、特点及变化趋势(Causes, characteristics and trend of antibiotic residues in aquaculture water)

水产养殖中抗生素的污染来源主要有:(1)水产养殖中直接使用的抗生素;(2)家禽粪/牛粪等水产饲料中的抗生素残留;(3)受污染的养殖用水中的抗生素。其中直接使用的抗生素是最重要的来源之一[14-15]。鱼类是全球贸易量最大的粮食商品之一,为人类的粮食安全和充足营养供应做出了重大贡献,目前野生鱼类捕捞量已趋平稳,能够持续大幅增长的用于人类消费的鱼类供应主要来源于水产养殖[16]。当前,世界范围内的水产养殖模式已从传统养殖系统向集约化养殖系统转变,导致高密度养殖现象,显著增加了感染细菌性疾病发生和传播的风险[17]。为了预防和治疗这些疾病,抗生素在水产养殖中得到了广泛的应用。此外,抗生素,特别是土霉素和氟苯尼考也被用作水产养殖生物的生长促进剂[18]。世界范围内水产养殖中抗生素的使用量显著增加,抗生素的施用方式主要有混合饲料饲喂法、沐浴法和池洒法,其中混合饲料饲喂是抗生素的常见施用途径,这些饲喂方式都容易导致抗生素在水产养殖环境中残留,严重污染养殖环境和养殖生物,增加养殖鱼类的抗生素暴露风险[19-20]。

近年来,在水产养殖水环境中频繁检出抗生素,主要包括磺胺类、四环素类以及氟喹诺酮类药物。表 1 列举了国内外部分养殖水体中检测频率和浓度较高的抗生素种类及其残留量。由数据可知,养殖水体中抗生素的残留量较高,大多在 $ng \cdot L^{-1}$ ~ $\mu g \cdot L^{-1}$ 水平。其中检测到磺胺类残留量最高达 7.42 $\mu g \cdot L^{-1}$,氟喹诺酮类最高达 958 $\mu g \cdot L^{-1}$,四环素类最高达 15.163 $\mu g \cdot L^{-1}$。

养殖水体中抗生素残留水平主要与水产养殖的空间分布、养殖生物种类、生长阶段以及季节等因素有关。在我国检测到较高抗生素残留量的养殖水体

表 1 养殖水体中抗生素浓度

Table 1 Concentration of antibiotics in aquaculture water

抗生素种类 Antibiotic type	养殖水体采样位置 Sampling location of aquaculture water	浓度/(ng·L^{-1}) Concentration/(ng·L^{-1})	参考文献 Reference
磺胺嘧啶 Sulfadiazine	中国茅尾海 Maowei Sea, China	ND ~ 28.60	[21]
	中国北部湾 Beibu Gulf, China	ND ~ 24.42	[22]
	中国杭州湾 Hangzhou Bay, China	0.86 ~ 2.67	[23]
	中国北江 Beijiang River, China	ND ~ 7 418.00	[24]
	中国洪湖 Lake Honghu, China	8.00 ~ 261.10	[25]
	中国桂林 Guilin, China	32.30 ~ 333.71	[26]
	韩国 Republic of Korea	ND ~ 5.69	[27]
	孟加拉国 Bangladesh	ND ~ 17.97	[28]
磺胺甲恶唑 Sulfamethoxazole	中国北部湾 Beibu Gulf, China	ND ~ 3.30	[22]
	中国杭州湾 Hangzhou Bay, China	2.25 ~ 15.17	[23]
	中国北江 Beijiang River, China	ND ~ 29.60	[24]
	中国洪湖 Lake Honghu, China	6.00 ~ 260.50	[25]
	中国桂林 Guilin, China	116.76 ~ 652.69	[26]
	中国黄海 Yellow Sea, China	ND ~ 3.43	[29]
	中国莱州湾 Laizhou Bay, China	0.60 ~ 1 273.70	[30]
	中国太湖 Tai Lake, China	ND ~ 7 189.10	[31]
恩诺沙星 Enrofloxacin	中国北江 Beijiang River, China	ND ~ 20.40	[24]
	中国桂林 Guilin, China	181.49 ~ 678.48	[26]
	中国黄海 Yellow Sea, China	ND ~ 995.02	[29]
	中国莱州湾 Laizhou Bay, China	0.31 ~ 82.25	[30]
	中国太湖 Tai Lake, China	ND ~ 183.61	[31]
	中国广州 Guangzhou, China	ND ~ 100.00	[32]
	马来西亚 Malaysia	ND ~ 958 000.00	[33]
诺氟沙星 Norfloxacin	中国北部湾 Beibu Gulf, China	4.31 ~ 97.30	[22]
	中国杭州湾 Hangzhou Bay, China	15.20 ~ 115.28	[23]
	中国桂林 Guilin, China	ND ~ 191.07	[26]
	中国黄海 Yellow Sea, China	ND ~ 8.73	[29]
	中国莱州湾 Laizhou Bay, China	ND ~ 72.37	[30]
	中国太湖 Tai Lake, China	ND ~ 210.57	[31]
	马来西亚 Malaysia	ND ~ 6 670.00	[33]
环丙沙星 Ciprofloxacin	中国北部湾 Beibu Gulf, China	5.42 ~ 182.00	[22]
	中国桂林 Guilin, China	135.57 ~ 247.64	[26]
	中国黄海 Yellow Sea, China	ND ~ 61.29	[29]
	中国莱州湾 Laizhou Bay, China	ND ~ 73.84	[30]
	马来西亚 Malaysia	ND ~ 131 000.00	[33]
	中国海陵岛 Hailing Island, China	ND ~ 186.00	[34]
	中国广东 Guangdong, China	15.80 ~ 61.80	[35]
土霉素 Oxytetracycline	中国杭州湾 Hangzhou Bay, China	12.35 ~ 38.33	[23]
	中国北江 Beijiang River, China	ND ~ 89.40	[24]
	中国黄海 Yellow Sea, China	ND ~ 41.03	[29]
	中国莱州湾 Laizhou Bay, China	ND ~ 175.02	[30]
	中国太湖 Tai Lake, China	ND ~ 198.83	[31]
	中国海陵岛 Hailing Island, China	ND ~ 15 163.00	[34]
	越南 Vietnam	200.00 ~ 250.00	[36]
	韩国 Republic of Korea	ND ~ 9 935.00	[37]

续表1

抗生素种类 Antibiotic type	养殖水体采样位置 Sampling location of aquaculture water	浓度/(ng·L^{-1}) Concentration/(ng·L^{-1})	参考文献 Reference
四环素 Tetracycline	中国杭州湾 Hangzhou Bay, China	9.89～34.11	[23]
	中国北江 Beijiang River, China	ND～303.00	[24]
	中国洪湖 Lake Honghu, China	98.50～1 019.20	[25]
	中国莱州湾 Laizhou Bay, China	ND～1.73	[30]
	中国太湖 Tai Lake, China	ND～250.63	[31]
	马来西亚 Malaysia	ND～73.00	[33]
	中国海陵岛 Hailing Island, China	ND～2 305.00	[34]
	越南 Vietnam	130.00～190.00	[36]
红霉素 Erythromycin	中国茅尾海 Maowei Sea, China	ND～1 290.00	[21]
	中国北部湾 Beibu Gulf, China	0.62～45.80	[22]
	中国北江 Beijiang River, China	1.00～68.80	[24]
	中国广州 Guangzhou, China	80.00～1 400.00	[32]
氟苯尼考 Florfenicol	中国北部湾 Beibu Gulf, China	ND～578.00	[22]
	中国杭州湾 Hangzhou Bay, China	0.48～47.97	[23]
	中国太湖 Tai Lake, China	ND～2 708.60	[31]
	中国广东 Guangdong, China	ND～1 282.00	[35]
	韩国 Republic of Korea	ND～1 600.00	[37]

主要分布于东部和南部,包括黄海、莱州湾、海陵岛和北江等地。这和我国水产养殖的空间分布有关,据报道东部和南部地区的养殖面积可达北部和西部地区的 600 倍,广东、山东、福建、江苏和湖北是产量最大的 5 个省份[19]。

不同养殖生物对抗生素的需求差异会影响养殖水体中抗生素残留水平。大菱鲆的抗病性较差,养殖中通常伴随着高剂量的抗生素使用,导致其养殖水体抗生素含量高于海参池和软体动物池[30]。大环内酯类药物仅在虾/蟹池中检测到,在鱼池中未检出,这是由于大环内酯类药物对藻类有较强毒性,可以控制高温期间在虾/蟹池经常发生的藻华[31]。王敏等[38]检测了鱼、虾、蟹养殖水体中抗生素的残留水平,抗生素检出种类情况为鱼(6 种)>虾(5 种)>蟹(3 种),其中诺氟沙星仅在虾池中检出,磺胺二甲嘧啶、磺胺甲恶唑和甲氧苄氨嘧啶仅在鱼池和虾池中检出,氧氟沙星和磺胺嘧啶仅在鱼池和蟹池中检出。李贞金等[39]在不同生物的养殖池中检出的抗生素种类也不相同,其中鱼池 10 种、虾池 9 种、蟹池仅 5 种。氟喹诺酮类在鱼池中的检出浓度远高于虾池和蟹池,喹乙醇在虾池中的检出浓度远高于鱼池和蟹池,磺胺甲恶唑仅在蟹池中被检出。养殖生物的不同生长阶段对抗生素的需求也有较大差异,幼年时期的抵抗力较差,需要更多的抗生素用于疾病防治和促进生长。而在成年时期会减少或停止抗生素的使用,以最大限度地减少水产品中抗生素的残留[21-22, 34]。抗生素在养殖水体中的残留量也受季节因素影响,夏季比冬季检测到的抗生素浓度更高,种类更多。夏季是水产养殖的主要季节,高温会导致水生生物疾病频发,抗生素用量增加[21, 25, 29-30, 40]。

1.2　养殖水环境中抗生素残留引发生态环境问题 (Antibiotic residues in aquaculture water may cause ecological and environmental problems)

水产养殖系统和周围水域之间存在交叉污染现象。养殖水体中抗生素的大量残留会对周围水域造成污染。养殖池塘中多种广泛用于水生生物的抗生素(如磺胺甲氧嘧啶、磺胺甲恶唑和环丙沙星)的检测浓度高于附近的河流[35, 40]。此外,开放水域养殖渔业的水源是从地表水或附近海水中收集的,而周边水体中由人为活动产生的污染物也会对养殖水体产生影响,包括医用抗生素(林可霉素、红霉素等)、咖啡因、布洛芬和工业化学品(防腐剂和全氟化合物)[40]。如果养殖池中含有高浓度抗生素的废水不加限制地排放到附近的水域中,将严重破坏相关水域生态系统的稳定性,而养殖池附近水域的水环境保护对养殖业公共健康也至关重要。

养殖水体中的抗生素残留最终会成为水产养殖生态系统的潜在生态风险。长期接触低浓度抗生素

会影响水生生物的生长和繁殖,造成慢性中毒,导致畸形或死亡,在养殖生物体中积累的抗生素通过食物链进入人体,并可能影响人体健康[41]。此外,水生环境中 ARGs 的迁移和转化可能比环境中的抗生素残留物危害更大。抗生素在养殖水体中的持续残留会导致 ARGs 的产生和富集,进而会使抗生素失效,水产养殖生物更容易感染疾病,导致养殖产业的巨大经济损失。而食用受 ARGs 污染的水产品或暴露在受污染的水生环境中可能会增加人类健康风险[42]。

2 鱼类肠道菌群功能(Fish gut microbiota function)

鱼类肠道菌群参与鱼类营养物质的消化、吸收和免疫防御等,能促进宿主的生长发育维持宿主的健康。

2.1 促进生长(Promote the growth of fish)

肠道菌群可通过促进宿主的能量获取直接促进鱼体生长,研究发现,梭菌科、纤毛菌科、动球菌科和毛螺菌科的细菌可以决定鱼体的生长速度,这些细菌与宿主互利共生[43]。研究证实花斑溪鳉、大西洋鳕鱼的生长速率与肠道菌群组成密切相关[44-45]。Tan 等[46]报道,从尼罗罗非鱼肠道分离出的 *Rummeli-ibacillusstabekisii* 菌株可以提高蛋白酶、木聚糖酶和纤维素酶的活性,这些酶可以帮助宿主消化蛋白质和糖类物质,提高营养物质利用率,促进鱼体的生长。此外,肠道菌群在脂质代谢中也发挥重要作用。Falcinelli 等[47]发现,在鼠李糖乳杆菌的作用下,斑马鱼肠道中厚壁菌丰度增加,放线菌丰度降低,这些肠道菌群的变化导致胆固醇和甘油三酯代谢相关基因(如 *fit2*、*agpat4*、*dgat2* 和 *mgll*)表达下调,最终调节宿主的脂质代谢。Semova 等[48]的研究显示,厚壁菌可以刺激肠上皮细胞中脂肪酸的摄取,导致肠细胞中脂滴的积累和膳食中脂肪酸在肠外组织中的积累。因此,鱼类肠道菌群可通过调节宿主蛋白质吸收、糖类吸收和脂质代谢在调节鱼体营养吸收方面发挥重要作用。

2.2 免疫功能(The immune function)

鱼类有复杂的免疫系统。第一道防线由皮肤和黏膜组成,为宿主提供屏障,并具有杀菌活性。第二道防线是先天免疫系统,第三条防线是适应性免疫系统。鱼类的肠道菌群是免疫系统的重要组成部分。

肠道菌群可作为鱼类免疫的第一道防线——直接屏障[49]。微生物生物膜在宿主的发育和功能中发挥着重要作用,并保护宿主免受病原体的侵害。Burtseva 等[50]从海洋鱼类肠道中分离出的生物发光细菌菌株可以在体外形成生物膜,这表明鱼类肠道菌群中也存在能够抵抗外来病原体的微生物生物膜系统。此外,肠道内的共生细菌可通过竞争或改变生态位和可用营养素等抑制肠道内机会性病原体的定植和增殖。例如,益生菌双歧杆菌通过肠道环境酸化(种间屏障效应)防止致病性大肠杆菌入侵[51]。肠道共生菌还可以产生细菌素和蛋白毒素,专门抑制相同或相似细菌物种的成员(种内屏障效应)生长或定植。

肠道菌群与鱼类的先天免疫和适应性免疫密切相关。鱼类肠道菌群可以通过调节肠道中免疫相关细胞的功能发挥免疫调节作用。研究表明,鱼类肠道菌群在肠道上皮细胞更新和成熟过程中发挥关键作用[52],肠道上皮细胞的更新和成熟是免疫反应过程的重要部分。与无菌斑马鱼相比,传统饲养的斑马鱼与上皮细胞增殖和先天免疫反应相关的基因表达量更高[53]。成熟的肠道黏膜可通过模式识别受体(PRRs,如 TOLL 样受体、RIG-I 样受体、NOD 样受体和 AIM2 样受体)区分病原体和共生菌,PRRs 能检测到细菌抗原并激活信号级联反应以调节免疫反应。例如,TOLL 样受体家族是 PRRs 的代表成员,能识别病原体中的保守结构,可以招募和调节免疫和炎症细胞,从而启动和介导全身免疫反应[54]。研究表明患有肠炎的石斑鱼肠道中弧菌、链球菌等病原体增加,激活 TOLL 样受体、RIG-I 样受体和 NOD 样受体信号通路[55]。在斑马鱼中,肠道共生细菌是中性粒细胞募集的主要来源,共生细菌通过 TLR/MyD88/NF-kB 信号通路诱导促炎细胞因子和抗病毒介质的表达[56]。从成年黑鲈肠道菌群中分离得到的 *Lactobacillus delbrueckii*s sp.,被喂食给黑鲈幼鱼以研究其对肠道免疫系统发育和分化的影响,观察到处理鱼的 T 细胞和嗜酸粒细胞数量显著高于对照鱼[57]。有研究表明在没有肠腔细菌的情况下,B 细胞和 T 细胞从肠道固有层迁移,同时免疫球蛋白 A 也不再分泌[54]。

2.3 增强鱼体抵抗环境污染物的能力(Enhance the ability of fish body to resist environmental pollutants)

外源性污染物的毒性可在肠道细菌代谢后降低。研究表明,菌群可将环境污染物生物催化转化,这些转化过程包括还原、水解、官能团去除、N-氧化物裂解、蛋白质水解和反硝化等[58]。研究证明,肠道细菌的生物转化能力可以有效降解多种污染物,如药品[59]、金属[60]、农药[61]以及多环芳烃[62]。

2.4 肠道菌群与疾病(Gut microbiota and disease)

正常情况下,鱼的肠道菌群始终保持动态平衡,

从而维持正常的生理功能。然而,环境的变化,如水温、食物类型、污染物接触、病毒和细菌感染等均可破坏肠道菌群的平衡和稳态,由此将可能导致病原菌的异常生长,与鱼类相关疾病的发生密切相关。

患红盖病的鲫鱼肠道菌群多样性和稳定性改变,条件致病菌包括弧菌、气单胞菌和希瓦氏菌丰度增加[63]。鳗鲡弧菌感染的香鱼肠道菌群多样性和均匀度下降,梭菌目增加,该目包括病原体艰难梭菌[64]。患疖病的圆口铜鱼肠道菌群多样性下降,病原体杀鲑气单胞菌显著增加[65]。患有肠炎的草鱼肠道中 *Dechloromonas* 和 *Methylocaldum* 等致病菌种类增加,进一步导致氨基酸代谢、外源性物质生物降解和代谢以及碳水化合物代谢增强,这可能会加剧肠炎的发展[66]。Parshukov 等[67]对患病虹鳟(皮肤表面溃疡、鱼鳍坏死、贫血和肠道炎症)的肠黏膜进行测序,发现患病虹鳟肠道中的主要细菌门是变形菌、放线菌、厚壁菌和软壁菌,而健康虹鳟鱼肠道中主要为拟杆菌和梭杆菌。患病罗非鱼(皮肤出血性败血症、眼球突出)肠道菌群多样性下降,变形菌门取代梭菌门成为最主要的门,弧菌属取代头孢菌属成为最主要的属[68]。Ye 等[69]发现,在高脂肪饮食下,斑马鱼肠道中不动杆菌、假单胞菌和气单胞菌的丰度显著增加。此外,不动杆菌的增加导致肠内分泌细胞的形态变化和营养不敏感状态,这导致代谢性疾病(包括肥胖和胰岛素抵抗)的发病率和严重程度更高。

3　抗生素对鱼类肠道菌群结构和功能的影响(Effects of antibiotics on intestinal structure and function of fish)

3.1　氟喹诺酮类抗生素(Fluoroquinolone antibiotics)

关于氟喹诺酮类抗生素对鱼类肠道菌群影响的研究主要集中在氟喹诺酮类抗生素对淡水鱼的短期暴露实验研究(表 2)。环境水平的恩诺沙星暴露会导致斑马鱼肠道中立克次氏体和假单胞菌减少,黄杆菌比例增加,此外,肠道菌群紊乱会进一步影响斑马鱼的免疫功能[70]。虹鳟给药恩诺沙星(25 mg·kg^{-1})5d 后,其肠道中拟杆菌属和支原体减少,梭菌属和鲸杆菌属增加[71]。高浓度环丙沙星(1 mg·L^{-1})会导致香鱼肠道中变形菌门、厚壁菌门和疣微菌门增加,放线菌门、拟杆菌门和软壁菌门减少,进一步导致肠道杯状细胞减少,免疫失调,肠上皮细胞坏死[72]。短期暴露于环境水平的诺氟沙星会导致大黄鱼肠道菌群多样性显著降低,变形菌门的相对丰度降低,但软壁菌门增加。从菌群功能的角度来看,诺氟沙星抑制细菌的代谢、细胞防御机制和信息转导过程,最终会抑制鱼体生长[73]。

3.2　四环素类抗生素(Tetracycline antibiotics)

四环素类抗生素对鱼类肠道菌群的研究比较充分,其中在环境中残留浓度较高的土霉素对鱼类肠道菌群的研究最集中。另外有研究报道四环素和强力霉素在不同的暴露方式下对肠道菌群结构和功能的影响(表 3)。斑马鱼暴露于环境水平的四环素(1 μg·L^{-1}和 100 μg·L^{-1})后,肠道菌群多样性增加,变形菌门、拟杆菌门以及厚壁菌门显著失调,拟杆菌门和厚壁菌门的比例增加,进而导致斑马鱼体质量增加[74]。四环素暴露金鱼 21 d,鱼肠道耐药菌比例增加,梭杆菌门取代厚壁菌门成为绝对优势菌群,鲸杆菌属增加,伟荣球菌属减少,菌群紊乱会进一步导致能量代谢失调,菌群耐药性增强[75]。无论是暴露还是给药方式的土霉素均能显著改变肠道菌群组成[76-83],导致致病菌增加,免疫和代谢功能失调。强力霉素暴露导致斑马鱼肠道菌群多样性减少,梭杆菌门减少,具有潜在毒性的丛毛单胞菌属增加[84]。

3.3　磺胺类抗生素(Sulfonamide antibiotics)

磺胺类抗生素的研究主要集中在磺胺甲恶唑和磺胺间甲氧嘧啶(表 4)。长期暴露于环境浓度磺胺甲恶唑(1 μg·L^{-1}和 5 μg·L^{-1})导致致病性黄杆菌的积累,此外,一些代谢途径,包括叶酸生物合成、氧化磷酸化和生物素代谢途径在暴露样品中显著富集[76]。磺胺甲恶唑(5、90 和 450 μg·L^{-1})暴露成年斑马鱼 3 周,会导致其肠道中变形菌门、拟杆菌门丰度增加,厚壁菌门减少,一些机会致病菌包括军团菌属和 *Clostridium sensustricto 13* 出现[85]。以不同剂量磺胺甲恶唑给药均能显著影响鱼体肠道菌群组成[80, 86-87]。此外,这些研究结果显示的肠道菌群结构变化并不一致,这可能受给药剂量、给药时间以及实验生物多方面因素的影响。磺胺间甲氧嘧啶(200 mg·kg^{-1}和 300 mg·kg^{-1})喂养尼罗罗非鱼 4 周,其肠道菌群丰富度显著下降,放线菌减少,厚壁菌门(芽孢杆菌科)增加,并显著增强了肠道菌群的抗生素抗性[88]。

3.4　其他种类抗生素(Other classes of antibiotics)

其他种类抗生素对鱼体肠道菌群结构和功能的影响也有研究(表 5),其中氟苯尼考[84, 89-91]研究较多。此外也有不少研究评价了抗生素混合物对鱼体肠道菌群的影响[92-93]。

表 2　氟喹诺酮类抗生素对鱼类肠道菌群结构和功能的影响

Table 2　Effects of fluoroquinolone antibiotics on the structure and function of fish intestinal microbiota

抗生素种类 Antibiotic type	抗生素浓度及暴露时间 Antibiotic concentration and exposure time	物种 Species	肠道菌群结构变化 Structural changes of intestinal microbiota	肠道菌群相关功能变化 Functional changes of intestinal microbiota	参考文献 Reference
恩诺沙星 Enrofloxacin	0.01、0.1、1、10、100 μg·L^{-1}; 10 d	斑马鱼 Zebrafish	黄杆菌目 Flavobacteriales ↑、立克次氏体目 Rickettsiales ↓、假单胞菌目 Pseudomonadales ↓	诱导免疫抑制 Inducing immune suppression	[70]
	25 mg·kg^{-1}; 5 d	虹鳟 *Oncorhynchus mykiss*	梭菌属 *Clostridium* ↑、鲸杆菌属 *Cetobacterium* ↑、拟杆菌属 *Bacteroides* ↓	细菌衍生脂肪酸减少 Bacteria-derived fatty acids decrease	[71]
环丙沙星 Ciprofloxacin	1 000 μg·L^{-1}; 7 d	香鱼 *Plecoglossus altivelis*	变形菌门 Proteobacteria ↑、厚壁菌门 Firmicutes ↑、疣微菌门 Verrucomicrobia ↑、放线菌门 Actinobacteria ↓、拟杆菌门 Bacteroidetes ↓、软壁菌门 Tenericutes ↓; 弯曲杆菌属 *Ancylobacter* ↑、链球菌属 *Streptococcus* ↑、普雷沃菌属 *Prevotella* ↓	杯状细胞减少, 免疫失调, 肠上皮细胞坏死 The number of goblet cells decreased, immune dysregulation, intestinal epithelial cell necrosis	[72]
诺氟沙星 Norfloxacin	0.1、10、100、1 000 μg·L^{-1}; 14 d	大黄鱼 Large yellow croaker	软壁菌门 Tenericutes ↑、变形菌门 Proteobacteria ↓	代谢和免疫功能失调, 抑制鱼的生长 Metabolic and immune dysfunction, fish growth is inhibited	[73]

表 3　四环素类抗生素对鱼类肠道菌群结构和功能的影响

Table 3　Effects of tetracycline antibiotics on the structure and function of fish intestinal microbiota

抗生素种类 Antibiotic type	抗生素浓度及暴露时间 Antibiotic concentration and exposure time	物种 Species	肠道菌群结构变化 Structural changes of intestinal microbiota	肠道菌群相关功能变化 Functional changes of intestinal microbiota	参考文献 Reference
四环素 Tetracycline	1、100 μg·L^{-1}; 30 d	斑马鱼 Zebrafish	变形菌门 Proteobacteria ↑、拟杆菌门 Bacteroidetes ↓、厚壁菌门 Firmicutes ↓	脂质代谢失调, 体质量增加 Dysregulation of lipid metabolism and weight gain	[74]
	0.285、2.85 μg·L^{-1}; 21 d	金鱼 Goldfish	梭杆菌门 Fusobacteria ↑、厚壁菌门 Firmicutes ↓; 鲸杆菌属 *Cetobacterium* ↑、伟荣球菌属 *Erysipellotriceae* ↓	菌群耐药性增强, 能量代谢失调 Bacterial resistance increased, energy metabolism disorders	[75]

续表 3

抗生素种类 Antibiotic type	抗生素浓度及暴露时间 Antibiotic concentration and exposure time	物种 Species	肠道菌群结构变化 Structural changes of intestinal microbiota	肠道菌群相关功能变化 Functional changes of intestinal microbiota	参考文献 Reference
土霉素 Oxytetracycline	1、5 μg·L^{-1}; 90 d	斑马鱼 Zebrafish	黄杆菌属 *Flavobacterium*↑	病原菌定植,菌群耐药性增强,代谢紊乱 Pathogen colonization, bacterial resistance increased, metabolic disorders	[76]
	0.42 μg·L^{-1}; 42 d	斑马鱼 Zebrafish	梭杆菌门 Fusobacteria↑、CKC4 门↑、变形菌门 Proteobacteria↓、浮霉菌门 Planctomycetes↓	免疫功能受损,引发肠道炎症反应 Immune function is impaired, causing intestinal inflammation	[77]
	10、10 000 μg·L^{-1}; 60 d	斑马鱼 Zebrafish	α-变形菌纲 Alphaproteobacteria↑、放线菌纲 Actinobacteria↑、γ-变形菌纲 Gammaproteobacteria↓	代谢紊乱 Metabolic disorders	[78]
	10 000 μg·L^{-1}; 5 d	斑马鱼 Zebrafish	假单胞菌属 *Pseudomonas*↑、鲸杆菌属 *Cetobacterium*↓、芽孢杆菌属 *Bacillus*↓	能量代谢失调 Dysregulation of energy metabolism	[79]
	80 mg·kg^{-1}; 42 d	斑马鱼 Zebrafish	*CKC4* 门↑;肠球菌属 *Enterococcus*↑、气单胞菌属 *Aeromonas*↑	免疫和能量代谢失调,引发肠道炎症 Immune and energy metabolism are disrupted, and intestinal inflammation is triggered	[80]
	100 mg·kg^{-1}; 8 d	尼罗罗非鱼 Nile tilapia	梭杆菌门 Fusobacteria↑、变形菌门 Proteobacteria↓、放线菌门 Actinobacteria↓;邻单胞菌属 *Plesiomonas*↑	病原菌定植,菌群耐药性增强 Pathogen colonization, bacterial resistance increased	[81]
	80 mg·kg^{-1}; 35 d	尼罗罗非鱼 Nile tilapia	微杆菌属 *Microbacterium*↑、*Chlamydiae*↑、邻单胞菌属 *Plesiomonas*↑、*Bosea* 属↑、不动杆菌属 *Acinetobacter*↑、军团菌属 *Legionella*↑、芽孢杆菌属 *Bacillus*↑	免疫系统受损,能量代谢失调,生长性能降低,存活率降低 The immune system are impaired, energy metabolism is maladjusted, growth performance is reduced, and survival rate is reduced	[82]
	100 mg·kg^{-1}; 5 d	虹鳟 Rainbow trout	软壁菌门 Tenericutes↑、厚壁菌门 Firmicutes↑、梭杆菌门 Fusobacteria↓、变形菌门 Proteobacteria↓	代谢紊乱 Metabolic disorders	[83]
强力霉素 Doxycycline	10、30、100 μg·L^{-1}; 21 d	斑马鱼 Zebrafish	梭杆菌门 Fusobacteria↓;丛毛单胞菌属 *Comamonas*↑	病原菌定植 Colonization of pathogenic bacteria	[84]

表 4　磺胺类抗生素对鱼类肠道菌群结构和功能的影响

Table 4　Effects of sulfonamides antibiotics on the structure and function of fish intestinal microbiota

抗生素种类 Antibiotic type	抗生素浓度及暴露时间 Antibiotic concentration and exposure time	物种 Species	肠道菌群结构变化 Structural changes of intestinal microbiota	肠道菌群相关功能变化 Functional changes of intestinal microbiota	参考文献 Reference
磺胺甲恶唑 Sulfamethoxazole	1、5 μg·L^{-1}; 90 d	斑马鱼 Zebrafish	黄杆菌属 *Flavobacterium*↑	病原菌定植,菌群耐药性增强,代谢紊乱 Pathogen colonization, bacterial resistance increased, metabolic disorders	[76]
	100 mg·kg^{-1}; 42 d	斑马鱼 Zebrafish	*CKC4* 门↓;芽孢杆菌科 Bacillaceae↑、梭菌科 Clostridiaceae↑	抗氧化系统受损,能量代谢失调,鱼体质量增加 The antioxidant system is damaged, the energy metabolism is maladjusted, and the fish gain weight	[80]
	5、90、450 μg·L^{-1}; 21 d	斑马鱼 Zebrafish	变形菌门 Proteobacteria↑、拟杆菌门 Bacteroidetes↑、厚壁菌门 Firmicutes↓;军团菌属 *Legionella*↑、*Clostridium sensustricto 13*↑、*Hydrobacter*↑、葡萄球菌属 *Staphylococcus*↓、气单胞菌属 *Aeromonas*↓	脂质代谢失调,杯状细胞数量减少,肠上皮细胞脱落溶解 Lipid metabolism is maladjusted, the number of goblet cells is reduced, and intestinal epithelial cells are exfoliated and dissolved	[85]
	3 000 mg·kg^{-1}; 56 d	加州鲈 *Micropterus salmoides*	梭杆菌门 Fusobacteria↑、螺旋体门 Spirochaete↑、蓝藻菌门 Cyanobacteria↓、栖热菌门 Thermophilic↓;鲸杆菌属 *Cetobacterium*↑、螺旋体属 *Spirochaeta*↑、邻单胞菌属 *Plesiomonas*↓、*Mangrovibacter*↓、希瓦氏菌属 *Shewanella*↓、肠球菌属 *Enterococcus*↓、双歧杆菌属 *Bifidobacterium*↓	诱导氧化应激、炎症和细胞凋亡,器官指数和体质量增加 Induce oxidative stress, inflammation and apoptosis, organ index and body weight gain	[86]
	20、200、1 000 mg·kg^{-1}; 28 d	尼罗罗非鱼 Nile tilapia	梭杆菌门 Fusobacteria↑、变形菌门 Proteobacteria↓	脂质代谢失调,影响生长性能 Lipid metabolism is maladjusted and growth performance is affected	[87]
磺胺间甲氧嘧啶 Sulfamonomethoxine	200、300 mg·kg^{-1}; 28 d	尼罗罗非鱼 Nile tilapia	厚壁菌门 Firmicutes↑、放线菌门 Actinobacteria↓	破坏肠道菌群稳定性,菌群耐药性增强 Damage the stability of intestinal microbiota, bacterial resistance increased	[88]

表 5　其他抗生素对鱼类肠道菌群结构的功能的影响

Table 5　Effects of other antibiotics on the structure and function of fish intestinal microbiota

抗生素种类 Antibiotic type	抗生素浓度及暴露时间 Antibiotic concentration and exposure time	物种 Species	肠道菌群结构变化 Structural changes of intestinal microbiota	肠道菌群相关功能变化 Functional changes of intestinal microbiota	参考文献 Reference
氟苯尼考 Florfenicol	10、30、100 μg·L^{-1}; 21 d	斑马鱼 Zebrafish	变形菌门 Proteobacteria↑、梭杆菌门 Fusobacteria↓;布劳特氏菌属 *Blautia*↑、埃希氏杆菌属 *Escherichia-Shigella*↑、多尔氏菌属 *Dorea*↑、叶瘤杆菌属 *Phyllobacterium*↑	病原菌定植,能量代谢失调 Pathogen colonization, energy metabolism disorders	[84]
	10 mg·kg^{-1}; 10 d	布氏鲳鲹 *Trachinotus blochii*	变形菌门 Proteobacteria↑、广古菌门 Euryarchaeota↓、厚壁菌门 Firmicutes↓;弧菌属 *Vibrio*↑、肠弧菌属 *Enterovibrio*↑、发光菌属 *Photobacterium*↑、假单胞菌属 *Pseudomonas*↑、希瓦氏菌属 *Shewanella*↑、沙雷氏菌属 *Serratia*↓、甲烷杆菌属 *Methanobacterium*↓、不动杆菌属 *Acinetobacter*↓、芽孢杆菌属 *Bacillus*↓	病原菌定植,菌群耐药性增强 Pathogen colonization, bacterial resistance increased	[89]
	2 000 mg·kg^{-1};12 d	大西洋鲑鱼 Atlantic salmon	变形菌门 Proteobacteria↑、放线菌门 Actinobacteria↑、拟杆菌门 Bacteroidetes↑、软壁菌门 Tenericutes↓	肠道菌群稳定性遭到破坏 The stability of intestinal microbiota is destroyed	[90]
	500 mg·kg^{-1}; 3、6、10 d	斑点叉尾鮰 Channel catfish	邻单胞菌属 *Plesiomonas*↑、志贺氏杆菌属 *Shigella*↑、气单胞菌属 *Aeromonas*↑	病原菌定植 Colonization of pathogenic bacteria	[91]
红霉素和氨苄西林 Erythromycin and Ampicillin	3 900μg·L^{-1}红霉素 Erythromycin; 3 125 μg·L^{-1}氨苄西林 Ampicillin;30 d	青鳉 *Oryzias latipes*	变形菌门 Proteobacteria↑、梭杆菌门 Fusobacteria↓;维氏气单胞菌 *Aeromonasveronii*↑、副溶血弧菌 *Vibrio parahaemolyticus*↑	免疫失调,诱发炎症 Immune dysfunction, inducing inflammation	[92]
甲硝唑、硫酸新霉素和万古霉素 Metronidazole, neomycin sulfate and vancomycin	4 000 mg·kg^{-1}甲硝唑 Metronidazole; 4 000 mg·kg^{-1}硫酸新霉素 Neomycin sulfate; 2 000 mg·kg^{-1}万古霉素 Vancomycin;6 d	杂交石斑鱼 Hybrid grouper	拟杆菌门 Bacteroidetes↑、厚壁菌门 Firmicutes↓;不动杆菌属 *Acinetobacter*↓、芽孢杆菌属 *Bacillus*↓、梭菌属 *Clostridium*↓、雷尔氏菌属 *Ralstonia*↓	脂质代谢、能量代谢失调 Dysregulation of lipid metabolism and energy metabolism	[93]

抗生素主要用于杀灭病原菌,有时也用做生长促进剂,但大量的研究证实抗生素在使用时会严重破坏肠道共生菌,这些菌在肠道定植抗力(抵抗病原体的能力)、免疫调节以及代谢等方面发挥重要作用,所以会进一步导致病原菌定植,肠道菌群多样性和代谢活性改变,从而影响宿主生理功能。抗生素通过影响肠道菌群的结构和功能,会进一步导致鱼体内抗氧化系统和免疫系统失调,诱发炎症反应,代谢紊乱,生长性能受到影响等。综上所述,抗生素能通过影响肠道菌群的结构和功能影响鱼体的健康。

4 抗生素对鱼类抗生素抗性组的影响(Effect of antibiotics on antibiotic resistome of fish)

抗生素抗性组,即抗生素抗性基因组,是一组编码具有抵抗抗生素作用蛋白质的微生物基因集。抗生素在养殖水环境中的长期残留导致水产养殖环境中抗性菌的出现,鱼类病原体的抗性能力增加。据报道,从世界各地的鱼类,如斑马鱼、金鱼、鲤鱼、沙丁鱼和银牙鱼等都分离得到了抗性病原菌,有许多表现出多重耐药性[94-98]。肠道菌群一直被视为 ARGs 的关键储库,在一些选择压力下如抗生素暴露,会导致 ARGs 的急剧富集,进而导致肠道中抗生素抗性菌的富集,这反过来会导致治疗无效。此外肠道菌群成员间还可以进行 ARGs 的交换,从而传播抗生素抗性组[99]。

4.1 抗生素诱导抗性基因富集(Antibiotic induced enrichment of resistance genes)

恩诺沙星暴露斑马鱼 10 d,通过 qPCR 技术检测到肠道中 7 种氟喹诺酮类抗性基因(*qnrA*、*catA1*、*cmeA*、*cmx(A)*、*mexF*、*mexE* 和 *cmlA1*)显著富集[70]。四环素暴露金鱼 3 周,检测到肠道中编码四环素外排基因(*tetA*、*tetG*、*tetL* 和 *tetZ*)以及磺胺类抗性基因(*sul1*)丰度显著增加[75]。土霉素和磺胺甲恶唑暴露斑马鱼 4 个月后,通过宏基因组技术检测到肠道中四环素类抗性基因(*tetX6*)以及磺胺类抗性基因(*sul2*)显著富集[76]。土霉素喂养尼罗罗非鱼 8 d,导致肠道中抗性基因 *tetA*、*tetM* 显著富集,并与条件致病菌邻单胞菌呈正相关[81]。氟苯尼考和土霉素的大量使用导致大西洋鲑鱼肠道中氟苯尼考和土霉素抗性细菌显著富集,另外还检测到对 8 种抗生素显示出抗性的“超级耐药”细菌,大多数抗性菌株中检测到氯霉素类抗性基因(*floR*、*fexA*)和四环素类抗性基因(*tetA*、*tetB*、*tetE*、*tetH*、*tetL*、*tet34* 和 *tet35*)[100]。口服氟苯尼考的细鳞肥脂鲤肠道菌群中 ARGs 总相对丰度显著增加,属于多药类、氯霉素类、氟喹诺酮类、氨基香豆素类、四环素类和肽类的抗性基因显著富集[101]。这些研究均证实抗生素能够导致鱼体肠道中 ARGs 显著富集。其中,所有的研究都表明使用一种特定抗生素能够使鱼类肠道菌群产生对同类抗生素的抗性,包括恩诺沙星暴露增加鱼类肠道中氟喹诺酮类抗性基因的相对丰度,四环素和土霉素的使用显著富集四环素类抗性基因,使用氟苯尼考能够显著富集氯霉素类抗性基因。但抗生素使用和抗性基因产生之间的关系并非如此简单,一种特定抗生素不仅可以产生对同类抗生素的抗性,还可以产生对其他类抗生素的抗性,即抗生素具有潜在“协同选择”作用[102]。这主要与交叉耐药和共耐药有关。当一个抗性基因可以对多种抗生素产生抗性时,就会发生交叉耐药[103]。共耐药是指多种抗性基因可能存在于同一个可移动遗传元件(MGE)上,如阿莫西林和甲氧苄啶抗性基因[104]。因此,使用一种抗生素治疗可能对另一种抗生素产生抗性。部分关于抗生素对鱼类肠道抗性基因富集的研究也体现了抗生素对 ARGs 的“协同选择”作用,包括四环素和土霉素的使用能够富集磺胺类抗性基因,氟苯尼考和土霉素的大量使用导致鱼肠道中出现对 8 种抗生素显示出抗性的“超级耐药”细菌以及口服氟苯尼考使多药类、氟喹诺酮类和四环素类抗性基因显著富集。

4.2 抗生素诱导抗性基因转移(Antibiotic induced resistance gene transfer)

因自发基因突变产生 ARGs 并不会造成抗性基因的广泛传播,水平基因转移(horizontal gene transfer, HGT)是导致 ARGs 传播和扩散的主要因素,环境选择压力和由 MGE(整合子、质粒和转座子等)介导的 HGT 是细菌获得外源抗性基因的主要原因[105]。HGT 主要有接合、转导和自然转化 3 种类型[106]。接合转移最为常见,ARGs 通过接合转移可在不同种属的微生物间传播[107]。HGT 使更多的细菌可以获得 ARGs,甚至打破了特定微生物生存环境中环境(非致病性)细菌和病原体之间的物种屏障[108]。

研究表明,抗生素是促进抗性基因水平转移的主要驱动因素之一。氟苯尼考和土霉素的大量使用导致大西洋鲑鱼肠道中多重耐药菌的富集,几乎 100% 耐药菌株检测到典型的 MGE-1 类整合子,也有研究在口服氟苯尼考的细鳞肥脂鲤肠道菌群中检测到 MGE 的总相对丰度显著增加,这都表明抗生

素增加了 MGE 介导的鱼肠道 ARGs 水平转移的可能性,导致 ARGs 在水产养殖系统中的富集和传播[97-98]。此外,还有研究在大西洋鲑鱼养殖场中发现,在大量使用抗生素后鱼类肠道菌群中携带 ARGs 的 1 类整合子显著富集[109]。

目前抗生素对鱼类肠道中 ARGs 转移的影响研究主要集中在对 MGE 的定量分析,具体的转移过程以及转移机制并不明确。因此未来抗生素选择压力下的 ARGs 转移相关研究应与接合转移实验模型及相关技术相结合明确转移过程和转移机制。另外噬菌体已被证明更适合作为 ARGs 转移的载体,这也表明转导在 HGT 过程中发挥重要作用[110]。目前只有少数研究对抗生素与噬菌体 ARGs 转移之间的关系进行了探讨。研究表明抗生素治疗增强了人类和小鼠肠道中携带 ARGs 的噬菌体数量[111-112]。然而,关于 ARGs 在鱼类噬菌体基因组中的分布特征以及噬菌体介导的 HGT 在鱼体内的作用机制,仍存在许多不确定性,鲜有相关研究报道。

4.3　鱼类抗生素抗性问题的健康风险研究(Health risk of antibiotic resistance in fish)

由于过度使用或滥用抗生素,会导致越来越多的抗性菌和 ARGs 出现。肠道微生物群作为一个与环境“半隔离”但与应用的抗生素直接接触的系统,是来自不同环境(包括人类临床环境)的细菌之间发生相互作用的理想场所[87]。现已在鱼类病原菌(沙门氏气单胞菌、迟缓爱德华氏菌、鳗鲡弧菌、嗜水气单胞菌、鱼型链球菌和鱼巴氏杆菌等)中检测到 ARGs 的普遍存在[113-114],其中一些病原体,例如爱德华氏菌、气单胞菌和链球菌,可以感染人类并产生人畜共患感染[115-116]。ARGs 的转移不受物种屏障的限制,人类可能通过受感染的鱼或鱼类生存环境直接接触到抗生素抗性菌和 ARGs。另外,鱼类作为人类的食物来源之一,其体内残留的抗生素或抗生素抗性菌可能因其被人类摄入而经由食物链传播最终到人类。鱼类细菌和人类病原体之间的 ARGs 可能存在双向流动,导致高风险 ARGs 在人群中广泛传播,会导致人类健康风险。在鱼和人类致病性气单胞菌以及住院患者分离的大肠杆菌中出现了类似的 *IncU* 不相容组质粒,其中含有抗性基因(*Tn1721 TetA*)决定簇和 1 类整合子[117-118]。鱼体中水生希瓦氏菌、发光杆菌、气单胞菌和弧菌与大量人类革兰氏阴性病原菌(如大肠杆菌和克雷伯菌)共享喹诺酮类抗性基因 *qnrA*、*qnrS* 和 *qnrVC*[119]。鱼类病原体(如鲁克氏菌、气单胞菌和爱德华氏菌)和人类病原体(例如鼠疫菌、沙门氏菌和霍乱弧菌)共同具有 *IncA/C* 多药耐药质粒[120-122]。这些研究均表明鱼类细菌和人类病原体之间的 ARGs 可能存双向传递过程。抗性基因转移最终将导致抗生素抗性(药物无法抑制细菌生长,失去用于治疗细菌感染能力的情况)问题,已成为全球范围的一个重要的公共卫生问题。

5　结论与展望(Conclusion and prospect)

正常情况下,肠道菌群处于动态平衡状态,益生菌占主导地位,与中性菌、致病菌相互制约和相互依存,保持肠道正常运转。目前大量研究证明环境水平的抗生素会严重破坏鱼体肠道生态平衡,并伴随着鱼体代谢和免疫能力的改变,但未能阐明其中的因果关系,缺乏系统的机制研究。同种抗生素导致的菌群变化结果并不一致,因此未来需要进一步建立系统的实验方案,从更深层次的分子机制探索抗生素与鱼类肠道菌群以及生理功能之间的关系,使相关研究更加标准化,增加结果的可信度和说服力。目前抗生素导致鱼类肠道 ARGs 富集和转移的相关研究也主要集中于对 ARGs 和 MGE 种类和相对丰度的基础调查,缺乏对 ARGs 富集和转移机制的进一步探索。此外,自然水环境中含有多种抗病毒药、重金属、微塑料、农药和人工甜味剂等污染物,这些污染物已被证实对肠道菌群结构和 ARGs 转移产生影响。当前研究多集中于单一污染物对肠道菌群以及 ARGs 的影响,鲜有从抗生素与其他污染物共污染角度研究肠道菌群结构和功能变化以及 ARGs 的传播和转移问题,尤其是污染物共选择压力的机制尚不明确。未来需要重视抗生素和其他污染物共污染对生物肠道菌群和 ARGs 的影响以及 ARGs 在水产养殖环境中传播带来的生态和健康风险,为全面评价水产养殖环境中的抗生素等污染物影响 ARGs 转移和扩散带来的生态健康风险提供科学依据,为医疗、农业和水产养殖业中抗生素的合理使用提供科学指导,有利于实现“绿色、健康、安全”的水产养殖业发展模式。

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参考文献(References):

[1] Preena P, Swaminathan T R, Kumar V J R, et al. Antimi-

crobial resistance in aquaculture: A crisis for concern [J]. Biologia, 2020, 75: 1497-1517

[2] Shao Y T, Wang Y P, Yuan Y W, et al. A systematic review on antibiotics misuse in livestock and aquaculture and regulation implications in China [J]. The Science of the Total Environment, 2021, 798: 149205

[3] Lulijwa R, Rupia E J, Alfaro A C. Antibiotic use in aquaculture, policies and regulation, health and environmental risks: A review of the top 15 major producers [J]. Reviews in Aquaculture, 2020, 12(2): 640-663

[4] Álvarez J, Fernández Real J M, Guarner F, et al. Gut microbes and health [J]. Gastroenterology and Hepatology, 2021, 44(7): 519-535

[5] Li Z, Li M, Zhang Z Y, et al. Antibiotics in aquatic environments of China: A review and meta-analysis [J]. Ecotoxicology and Environmental Safety, 2020, 199: 110668

[6] Prasannamedha G, Kumar P. A review on contamination and removal of sulfamethoxazole from aqueous solution using cleaner techniques: Present and future perspective [J]. Journal of Cleaner Production, 2019, 250: 119553

[7] Andersson D I, Hughes D. Microbiological effects of sublethal levels of antibiotics [J]. Nature Reviews Microbiology, 2014, 12(7): 465-478

[8] Shun-Mei E, Zeng J M, Yuan H, et al. Sub-inhibitory concentrations of fluoroquinolones increase conjugation frequency [J]. Microbial Pathogenesis, 2018, 114: 57-62

[9] Tamminen M, Karkman A, Lõhmus A, et al. Tetracycline resistance genes persist at aquaculture farms in the absence of selection pressure [J]. Environmental Science & Technology, 2011, 45(2): 386-391

[10] Shuai M L, Zhang G Q, Zeng F F, et al. Human gut antibiotic resistome and progression of diabetes [J]. Advanced Science, 2022, 9(11): e2104965

[11] Naylor R L, Hardy R W, Buschmann A H, et al. A 20-year retrospective review of global aquaculture [J]. Nature, 2021, 591(7851): 551-563

[12] Zeng S Z, Hou D W, Liu J, et al. Antibiotic supplement in feed can perturb the intestinal microbial composition and function in Pacific white shrimp [J]. Applied Microbiology and Biotechnology, 2019, 103(7): 3111-3122

[13] World Health Organization. New report calls for urgent action to avert antimicrobial resistance crisis 2019 [R]. Geneva: World Health Organization, 2019

[14] Hossain A, Habibullah-Al-Mamun M, Nagano I, et al. Antibiotics, antibiotic-resistant bacteria, and resistance genes in aquaculture: Risks, current concern, and future thinking [J]. Environmental Science and Pollution Research International, 2022, 29(8): 11054-11075

[15] Li F P, Huang J, Wang M Z, et al. Sources, distribution and dynamics of antibiotics in *Litopenaeusvannamei* farming environment [J]. Aquaculture, 2021, 545: 737200

[16] Food and Agriculture Organization. The state of world fisheries and aquaculture: Opportunities and challenges 2016 [R]. Rome: Food and Agriculture Organization of the United Nations, 2016

[17] Santos L, Ramos F. Antimicrobial resistance in aquaculture: Current knowledge and alternatives to tackle the problem [J]. International Journal of Antimicrobial Agents, 2018, 52(2): 135-143

[18] Reda R M, Ibrahim R E, Ahmed E N G, et al. Effect of oxytetracycline and florfenicol as growth promoters on the health status of cultured *Oreochromis niloticus* [J]. The Egyptian Journal of Aquatic Research, 2013, 39(4): 241-248

[19] Liu X, Steele J C, Meng X Z. Usage, residue, and human health risk of antibiotics in Chinese aquaculture: A review [J]. Environmental Pollution, 2017, 223: 161-169

[20] Okocha R C, Olatoye I O, Adedeji O B. Food safety impacts of antimicrobial use and their residues in aquaculture [J]. Public Health Reviews, 2018, 39: 21

[21] Zhang R L, Kang Y R, Zhang R J, et al. Occurrence, source, and the fate of antibiotics in mariculture ponds near the Maowei Sea, South China: Storm caused the increase of antibiotics usage [J]. The Science of the Total Environment, 2021, 752: 141882

[22] Zhang R L, Pei J Y, Zhang R J, et al. Occurrence and distribution of antibiotics in mariculture farms, estuaries and the coast of the Beibu Gulf, China: Bioconcentration and diet safety of seafood [J]. Ecotoxicology and Environmental Safety, 2018, 154: 27-35

[23] Yuan J L, Ni M, Liu M, et al. Occurrence of antibiotics and antibiotic resistance genes in a typical estuary aquaculture region of Hangzhou Bay, China [J]. Marine Pollution Bulletin, 2019, 138: 376-384

[24] Zhong Y H, Chen Z F, Dai X X, et al. Investigation of the interaction between the fate of antibiotics in aquafarms and their level in the environment [J]. Journal of Environmental Management, 2018, 207: 219-229

[25] Wang Z, Du Y, Yang C, et al. Occurrence and ecological hazard assessment of selected antibiotics in the surface waters in and around Lake Honghu, China [J]. The Science of the Total Environment, 2017, 609: 1423-1432

[26] Chen J L, Huang L L, Wang Q, et al. Antibiotics in aquaculture ponds from Guilin, South of China: Occurrence, distribution, and health risk assessment [J]. Environmental Research, 2022, 204(Pt B): 112084

[27] Kim H Y, Lee I S, Oh J E. Human and veterinary pharmaceuticals in the marine environment including fish farms in Korea [J]. Science of the Total Environment, 2017, 579: 940-949

[28] Hossain A, Nakamichi S, Habibullah-Al-Mamun M, et al. Occurrence, distribution, ecological and resistance risks of antibiotics in surface water of finfish and shellfish aquaculture in Bangladesh [J]. Chemosphere, 2017, 188: 329-336

[29] Han Q F, Zhao S, Zhang X R, et al. Distribution, combined pollution and risk assessment of antibiotics in typical marine aquaculture farms surrounding the Yellow Sea, North China [J]. Environment International, 2020, 138: 105551

[30] Han Q F, Zhang X R, Xu X Y, et al. Antibiotics in marine aquaculture farms surrounding Laizhou Bay, Bohai Sea: Distribution characteristics considering various culture modes and organism species [J]. The Science of the Total Environment, 2021, 760: 143863

[31] Song C, Zhang C, Fan L M, et al. Occurrence of antibiotics and their impacts to primary productivity in fishponds around Tai Lake, China [J]. Chemosphere, 2016, 161: 127-135

[32] Chen H, Liu S, Xu X R, et al. Tissue distribution, bioaccumulation characteristics and health risk of antibiotics in cultured fish from a typical aquaculture area [J]. Journal of Hazardous Materials, 2018, 343: 140-148

[33] Thiang E L, Lee C W, Takada H, et al. Antibiotic residues from aquaculture farms and their ecological risks in Southeast Asia: A case study from Malaysia [J]. Ecosystem Health and Sustainability, 2021, 7(1): 1926337

[34] Chen H, Liu S, Xu X R, et al. Antibiotics in typical marine aquaculture farms surrounding Hailing Island, South China: Occurrence, bioaccumulation and human dietary exposure [J]. Marine Pollution Bulletin, 2015, 90(1-2): 181-187

[35] Shi B S, Cheng X J, Chen H Z, et al. Occurrence, source tracking and removal of antibiotics in recirculating aquaculture systems (RAS) in Southern China [J]. Journal of Environmental Management, 2022, 324: 116311

[36] Giang L T, Thien T L T. Determination of residual quantity of tetracycline antibiotics in shrimp pool water by UPLC-HRMS method [J]. Vietnam Journal of Chemistry, 2019, 57(6): 758-764

[37] Choi S, Sim W, Jang D, et al. Antibiotics in coastal aquaculture waters: Occurrence and elimination efficiency in oxidative water treatment processes [J]. Journal of Hazardous Materials, 2020, 396: 122585

[38] 王敏, 俞慎, 洪有为, 等. 5 种典型滨海养殖水体中多种类抗生素的残留特性[J]. 生态环境学报, 2011, 20(5): 934-939
Wang M, Yu S, Hong Y W, et al. Residual characterization of multi-categorized antibiotics in five typical aquaculture waters [J]. Ecology and Environmental Sciences, 2011, 20(5): 934-939(in Chinese)

[39] 李贞金, 张洪昌, 沈根祥, 等. 水产养殖水、沉积物中抗生素检测方法优化及残留特征研究[J]. 生态毒理学报, 2020, 15(1): 209-219
Li Z J, Zhang H C, Shen G X, et al. Optimization of antibiotic detection methods and residual characteristics in aquaculture water and sediment [J]. Asian Journal of Ecotoxicology, 2020, 15(1): 209-219(in Chinese)

[40] Lai W W P, Lin Y C, Wang Y H, et al. Occurrence of emerging contaminants in aquaculture waters: Cross-contamination between aquaculture systems and surrounding waters [J]. Water, Air, & Soil Pollution, 2018, 229(8): 249

[41] Limbu S M, Chen L Q, Zhang M L, et al. A global analysis on the systemic effects of antibiotics in cultured fish and their potential human health risk: A review [J]. Reviews in Aquaculture, 2021, 13(2): 1015-1059

[42] Amarasiri M, Sano D, Suzuki S. Understanding human health risks caused by antibiotic resistant bacteria (ARB) and antibiotic resistance genes (ARG) in water environments: Current knowledge and questions to be answered [J]. Critical Reviews in Environmental Science and Technology, 2020, 50: 2016-2059

[43] Chapagain P, Arivett B, Cleveland B M, et al. Analysis of the fecal microbiota of fast- and slow-growing rainbow trout (*Oncorhynchus mykiss*) [J]. BMC Genomics, 2019, 20(1): 788

[44] Forberg T, Sjulstad E B, Bakke I, et al. Correlation between microbiota and growth in Mangrove Killifish (*Kryptolebiasmarmoratus*) and Atlantic cod (*Gadus morhua*) [J]. Scientific Reports, 2016, 6: 21192

[45] Trinh L T T, Bakke I, Vadstein O. Correlations of age and growth rate with microbiota composition in Atlantic cod (*Gadus morhua*) larvae [J]. Scientific Reports, 2017, 7(1): 8611

[46] Tan H Y, Chen S W, Hu S Y. Improvements in the growth performance, immunity, disease resistance, and gut microbiota by the probiotic *Rummeliibacillusstabekisii* in Nile tilapia (*Oreochromis niloticus*) [J]. Fish & Shellfish Immunology, 2019, 92: 265-275

[47] Falcinelli S, Picchietti S, Rodiles A, et al. *Lactobacillus rhamnosus* lowers zebrafish lipid content by changing gut microbiota and host transcription of genes involved in lip-

id metabolism [J]. Scientific Reports, 2015, 5: 9336

[48] Semova I, Carten J D, Stombaugh J, et al. Microbiota regulate intestinal absorption and metabolism of fatty acids in the zebrafish [J]. Cell Host & Microbe, 2012, 12(3): 277-288

[49] Xiong J B, Nie L, Chen J. Current understanding on the roles of gut microbiota in fish disease and immunity [J]. Zoological Research, 2019, 40(2): 70-76

[50] Burtseva O, Baulina O, Zaytseva A, et al. *In vitro* biofilm formation by bioluminescent bacteria isolated from the marine fish gut [J]. Microbial Ecology, 2021, 81(4): 932-940

[51] Fukuda S, Toh H, Hase K, et al. Bifidobacteria can protect from enteropathogenic infection through production of acetate [J]. Nature, 2011, 469(7331): 543-547

[52] Darby T M, Naudin C R, Luo L P, et al. *Lactobacillus rhamnosus* GG-induced expression of leptin in the intestine orchestrates epithelial cell proliferation [J]. Cellular and Molecular Gastroenterology and Hepatology, 2020, 9(4): 627-639

[53] Rawls J F, Samuel B S, Gordon J I. Gnotobiotic zebrafish reveal evolutionarily conserved responses to the gut microbiota [J]. Proceedings of the National Academy of Sciences of the United States of America, 2004, 101(13): 4596-4601

[54] Pérez T, Balcázar J L, Ruiz-Zarzuela I, et al. Host-microbiota interactions within the fish intestinal ecosystem [J]. Mucosal Immunology, 2010, 3(4): 355-360

[55] Zhang W, Tan B P, Deng J M, et al. PRR-mediated immune response and intestinal flora profile in soybean meal-induced enteritis of pearl gentian groupers, *Epinephelusfuscoguttatus*♀ × *Epinepheluslanceolatus*♂[J]. Frontiers in Immunology, 2022, 13: 814479

[56] Galindo-Villegas J, García-Moreno D, de Oliveira S, et al. Regulation of immunity and disease resistance by commensal microbes and chromatin modifications during zebrafish development [J]. Proceedings of the National Academy of Sciences of the United States of America, 2012, 109(39): E2605-E2614

[57] Picchietti S, Fausto A M, Randelli E, et al. Early treatment with *Lactobacillus delbrueckii* strain induces an increase in intestinal T-cells and granulocytes and modulates immune-related genes of larval *Dicentrarchuslabrax* (L.) [J]. Fish & Shellfish Immunology, 2009, 26(3): 368-376

[58] Claus S P, Guillou H, Ellero-Simatos S. The gut microbiota: A major player in the toxicity of environmental pollutants? [J]. NPJ Biofilms and Microbiomes, 2016, 2: 16003

[59] Sousa T, Paterson R, Moore V, et al. The gastrointestinal microbiota as a site for the biotransformation of drugs [J]. International Journal of Pharmaceutics, 2008, 363(1-2): 1-25

[60] Collins S L, Patterson A D. The gut microbiome: An orchestrator of xenobiotic metabolism [J]. Acta Pharmaceutica Sinica B, 2020, 10(1): 19-32

[61] Velmurugan G, Ramprasath T, Swaminathan K, et al. Gut microbial degradation of organophosphate insecticides-induces glucose intolerance via gluconeogenesis [J]. Genome Biology, 2017, 18(1): 8

[62] van de Wiele T, Vanhaecke L, Boeckaert C, et al. Human colon microbiota transform polycyclic aromatic hydrocarbons to estrogenic metabolites [J]. Environmental Health Perspectives, 2005, 113(1): 6-10

[63] Li T T, Li H, Gatesoupe F J, et al. Bacterial signatures of "red-operculum" disease in the gut of crucian carp (*Carassius auratus*) [J]. Microbial Ecology, 2017, 74(3): 510-521

[64] Nie L, Zhou Q J, Qiao Y, et al. Interplay between the gut microbiota and immune responses of ayu (*Plecoglossusaltivelis*) during *Vibrio anguillarum* infection [J]. Fish & Shellfish Immunology, 2017, 68: 479-487

[65] Li T T, Long M, Ji C, et al. Alterations of the gut microbiome of largemouth bronze gudgeon (*Coreiusguichenoti*) suffering from furunculosis [J]. Scientific Reports, 2016, 6: 30606

[66] Tran N T, Zhang J, Xiong F, et al. Altered gut microbiota associated with intestinal disease in grass carp (*Ctenopharyngodonidellus*) [J]. World Journal of Microbiology and Biotechnology, 2018, 34(6): 71

[67] Parshukov A N, Kashinskaya E N, Simonov E P, et al. Variations of the intestinal gut microbiota of farmed rainbow trout, *Oncorhynchus mykiss* (Walbaum), depending on the infection status of the fish [J]. Journal of Applied Microbiology, 2019, 127(2): 379-395

[68] Ofek T, Lalzar M, Izhaki I, et al. Intestine and spleen microbiota composition in healthy and diseased tilapia [J]. Animal Microbiome, 2022, 4(1): 50

[69] Ye L H, Mueller O, Bagwell J, et al. High fat diet induces microbiota-dependent silencing of enteroendocrine cells [J]. eLife, 2019, 8: e48479

[70] Qiu W H, Liu T, Liu X J, et al. Enrofloxacin induces intestinal microbiota-mediated immunosuppression in zebrafish [J]. Environmental Science & Technology, 2022, 56(12): 8428-8437

[71] Parshukov A N, Fokina N N, Sukhovskaya I V, et al. Infection and antibiotic treatment have prolonged effects on

gut microbiota, muscle and hepatic fatty acids in rainbow trout (*Oncorhynchus mykiss*) [J]. Journal of Applied Microbiology, 2022, 133(3): 1709-1724

[72] Wu X Y, Xiong J B, Fei C J, et al. Prior exposure to ciprofloxacin disrupts intestinal homeostasis and predisposes ayu (*Plecoglossusaltivelis*) to subsequent *Pseudomonas plecoglossicida*-induced infection [J]. Zoological Research, 2022, 43(4): 648-665

[73] Wang X H, Hu M H, Gu H X, et al. Short-term exposure to norfloxacin induces oxidative stress, neurotoxicity and microbiota alteration in juvenile large yellow croaker *Pseudosciaenacrocea* [J]. Environmental Pollution, 2020, 267: 115397

[74] Keerthisinghe T P, Wang F, Wang M J, et al. Long-term exposure to TET increases body weight of juvenile zebrafish as indicated in host metabolism and gut microbiome [J]. Environment International, 2020, 139: 105705

[75] Jia J, Cheng M Q, Xue X, et al. Characterization of tetracycline effects on microbial community, antibiotic resistance genes and antibiotic resistance of *Aeromonas* spp. in gut of goldfish *Carassius auratus* Linnaeus [J]. Ecotoxicology and Environmental Safety, 2020, 191: 110182

[76] Kayani M U R, Yu K, Qiu Y S, et al. Environmental concentrations of antibiotics alter the zebrafish gut microbiome structure and potential functions [J]. Environmental Pollution, 2021, 278: 116760

[77] Zhou L, Limbu S M, Shen M L, et al. Environmental concentrations of antibiotics impair zebrafish gut health [J]. Environmental Pollution, 2018, 235: 245-254

[78] Almeida A R, Alves M, Domingues I, et al. The impact of antibiotic exposure in water and zebrafish gut microbiomes: A 16S rRNA gene-based metagenomic analysis [J]. Ecotoxicology and Environmental Safety, 2019, 186: 109771

[79] Almeida A R, Domingues I, Henriques I. Zebrafish and water microbiome recovery after oxytetracycline exposure [J]. Environmental Pollution, 2021, 272: 116371

[80] Zhou L, Limbu S M, Qiao F, et al. Influence of long-term feeding antibiotics on the gut health of zebrafish [J]. Zebrafish, 2018, 15(4): 340-348

[81] Payne C J, Turnbull J F, MacKenzie S, et al. Investigating the effect of an oxytetracycline treatment on the gut microbiome and antimicrobial resistance gene dynamics in Nile tilapia (*Oreochromis niloticus*) [J]. Antibiotics, 2021, 10(10): 1213

[82] Limbu S M, Zhang H, Luo Y, et al. High carbohydrate diet partially protects Nile tilapia (*Oreochromis niloticus*) from oxytetracycline-induced side effects [J]. Environmental Pollution, 2020, 256: 113508

[83] Roy Choudhury A, Park J Y, Kim D Y, et al. Exposure to oxy-tetracycline changes gut bacterial community composition in rainbow trout: A preliminary study [J]. Animals: An Open Access Journal from MDPI, 2021, 11(12): 3404

[84] Qian M R, Wang J M, Ji X F, et al. Sub-chronic exposure to antibiotics doxycycline, oxytetracycline or florfenicol impacts gut barrier and induces gut microbiota dysbiosis in adult zebrafish (*Daino rerio*) [J]. Ecotoxicology and Environmental Safety, 2021, 221: 112464

[85] Zheng Y, Wang Y F, Zheng M T, et al. Exposed to sulfamethoxazole induced hepatic lipid metabolism disorder and intestinal microbiota changes on zebrafish (*Danio rerio*) [J]. Comparative Biochemistry and Physiology Toxicology & Pharmacology, 2022, 253: 109245

[86] Xie S W, Yin P, Tian L X, et al. Interactions between dietary lipid levels and chronic exposure of legal aquaculture dose of sulfamethoxazole in juvenile largemouth bass *Micropterus salmoides* [J]. Aquatic Toxicology, 2020, 229: 105670

[87] Fang L X, Chen X, Shan X B, et al. Antibiotic accumulation, growth performance, intestinal diversification, and function of Nile tilapia (*Oreochromis niloticus*) feed by diets supplemented with different doses of sulfamethoxazole [J]. Environmental Science and Pollution Research, 2021, 28(46): 65255-65264

[88] Ming J C, Fu Z Y, Ma Z H, et al. The effect of sulfamonomethoxine treatment on the gut microbiota of Nile tilapia (*Oreochromis niloticus*) [J]. MicrobiologyOpen, 2020, 9 (11): e1116

[89] Sumithra T G, Sharma K S R, Gangadharan S, et al. Dysbiosis and restoration dynamics of the gut microbiome following therapeutic exposure to florfenicol in snubnose pompano (*Trachinotusblochii*) to aid in sustainable aquaculture production strategies [J]. Frontiers in Microbiology, 2022, 13: 881275

[90] Gupta S, Fernandes J, Kiron V. Antibiotic-induced perturbations are manifested in the dominant intestinal bacterial phyla of Atlantic salmon [J]. Microorganisms, 2019, 7(8): 233

[91] Wang E L, Yuan Z H, Wang K Y, et al. Consumption of florfenicol-medicated feed alters the composition of the channel catfish intestinal microbiota including enriching the relative abundance of opportunistic pathogens [J]. Aquaculture, 2019, 501: 111-118

[92] Yoon J B, Hwang S, Yang J H, et al. Dynamics of the gut microbiome and transcriptome in Korea native ricefish (*Oryziaslatipes*) during chronic antibiotic exposure [J].

Genes, 2022, 13(7): 1243

[93] Xu J, Xie S W, Chi S Y, et al. Short-term dietary antibiotics altered the intestinal microbiota and improved the lipid metabolism in hybrid grouper fed medium and high-lipid diets [J]. Aquaculture, 2022, 547: 737453

[94] Hossain S, Dahanayake P S, De Silva B C J, et al. Multidrug resistant *Aeromonas* spp. isolated from zebrafish (*Danio rerio*): Antibiogram, antimicrobial resistance genes and class 1 integron gene cassettes [J]. Letters in Applied Microbiology, 2019, 68(5): 370-377

[95] Preena P G, Arathi D, Raj N S, et al. Diversity of antimicrobial-resistant pathogens from a freshwater ornamental fish farm [J]. Letters in Applied Microbiology, 2020, 71(1): 108-116

[96] Delalay G, Berezowski J A, Diserens N, et al. An understated danger: Antimicrobial resistance in aquaculture and pet fish in Switzerland, a retrospective study from 2000 to 2017 [J]. Journal of Fish Diseases, 2020, 43(10): 1299-1315

[97] Deng Y Q, Xu L W, Chen H X, et al. Prevalence, virulence genes, and antimicrobial resistance of *Vibrio* species isolated from diseased marine fish in South China [J]. Scientific Reports, 2020, 10(1): 14329

[98] Naik O A, Shashidhar R, Rath D, et al. Characterization of multiple antibiotic resistance of culturable microorganisms and metagenomic analysis of total microbial diversity of marine fish sold in retail shops in Mumbai, India [J]. Environmental Science and Pollution Research International, 2018, 25(7): 6228-6239

[99] Santos L, Ramos F. Antimicrobial resistance in aquaculture: Current knowledge and alternatives to tackle the problem [J]. International Journal of Antimicrobial Agents, 2018, 52(2): 135-143

[100] Higuera-Llantén S, Vásquez-Ponce F, Barrientos-Espinoza B, et al. Extended antibiotic treatment in salmon farms select multiresistant gut bacteria with a high prevalence of antibiotic resistance genes [J]. PLoS One, 2018, 13(9): e0203641

[101] Sáenz J S, Marques T V, Barone R S C, et al. Oral administration of antibiotics increased the potential mobility of bacterial resistance genes in the gut of the fish *Piaractusmesopotamicus* [J]. Microbiome, 2019, 7(1): 24

[102] Pouwels K B, Muller-Pebody B, Smieszek T, et al. Selection and co-selection of antibiotic resistances among *Escherichia coli* by antibiotic use in primary care: An ecological analysis [J]. PLoS One, 2019, 14(6): e0218134

[103] Paul D, Chakraborty R, Mandal S M. Biocides and healthcare agents are more than just antibiotics: Inducing cross to co-resistance in microbes [J]. Ecotoxicology and Environmental Safety, 2019, 174: 601-610

[104] Pouwels K B, Freeman R, Muller-Pebody B, et al. Association between use of different antibiotics and trimethoprim resistance: Going beyond the obvious crude association [J]. The Journal of Antimicrobial Chemotherapy, 2018, 73(6): 1700-1707

[105] Li W Y, Zhang G S. Detection and various environmental factors of antibiotic resistance gene horizontal transfer [J]. Environmental Research, 2022, 212(Pt B): 113267

[106] Bello-López J M, Cabrero-Martínez O A, Ibáñez-Cervantes G, et al. Horizontal gene transfer and its association with antibiotic resistance in the genus *Aeromonas* spp. [J]. Microorganisms, 2019, 7(9): 363

[107] 朱光平, 薛晨晨, 范宏亮, 等. 环境中抗生素抗性基因研究进展[J]. 预防医学, 2020, 32(11): 1121-1125, 1129
Zhu G P, Xue C C, Fan H L, et al. Research progress of antibiotic resistance genes in environment [J]. Preventive Medicine, 2020, 32(11): 1121-1125, 1129(in Chinese)

[108] Martínez J L. Bottlenecks in the transferability of antibiotic resistance from natural ecosystems to human bacterial pathogens [J]. Frontiers in Microbiology, 2012, 2: 265

[109] Vásquez-Ponce F, Higuera-Llantén S, Parás-Silva J, et al. Genetic characterization of clinically relevant class 1 integrons carried by multidrug resistant bacteria (MDRB) isolated from the gut microbiota of highly antibiotic treated *Salmo salar* [J]. Journal of Global Antimicrobial Resistance, 2022, 29: 55-62

[110] Zhang Y, Guo Y J, Qiu T L, et al. Bacteriophages: Underestimated vehicles of antibiotic resistance genes in the soil [J]. Frontiers in Microbiology, 2022, 13: 936267

[111] Modi S R, Lee H H, Spina C S, et al. Antibiotic treatment expands the resistance reservoir and ecological network of the phage metagenome [J]. Nature, 2013, 499(7457): 219-222

[112] McInnes R S, McCallum G E, Lamberte L E, et al. Horizontal transfer of antibiotic resistance genes in the human gut microbiome [J]. Current Opinion in Microbiology, 2020, 53: 35-43

[113] Zhou A G, Xie S L, Tang H J, et al. The dynamic of the potential pathogenic bacteria, antibiotic-resistant bacteria, and antibiotic resistance genes in the water at different growth stages of grass carp pond [J]. Environmental Science and Pollution Research International, 2022, 29(16): 23806-23822

[114] Miller R A, Harbottle H. Antimicrobial drug resistance in fish pathogens [J]. Microbiology Spectrum, 2018, 6(1): 10. 1128/microbiolspec. ARBA-10. 1128/microbiolspec.

0017-2017

[115] Novotny L, Dvorska L, Lorencova A, et al. Fish: A potential source of bacterial pathogens for human beings [J]. VeterinarniMedicina, 2004, 49(9): 343-358

[116] Naviner M, Gordon L, Giraud E, et al. Antimicrobial resistance of *Aeromonas* spp. isolated from the growth pond to the commercial product in a rainbow trout farm following a flumequine treatment [J]. Aquaculture, 2011, 315(3-4): 236-241

[117] Rhodes G, Huys G, Swings J, et al. Distribution of oxytetracycline resistance plasmids between aeromonads in hospital and aquaculture environments: Implication of Tn1721 in dissemination of the tetracycline resistance determinant Tet A [J]. Applied and Environmental Microbiology, 2000, 66(9): 3883-3890

[118] Rhodes G, Parkhill J, Bird C, et al. Complete nucleotide sequence of the conjugative tetracycline resistance plasmid pFBAOT6, a member of a group of IncU plasmids with global ubiquity [J]. Applied and Environmental Microbiology, 2004, 70(12): 7497-7510

[119] Cabello F C, Godfrey H P, Tomova A, et al. Antimicrobial use in aquaculture re-examined: Its relevance to antimicrobial resistance and to animal and human health [J]. Environmental Microbiology, 2013, 15(7): 1917-1942

[120] Douard G, Praud K, Cloeckaert A, et al. The *Salmonella* genomic island 1 is specifically mobilized in trans by the *IncA*/C multidrug resistance plasmid family [J]. PLoS One, 2010, 5(12): e15302

[121] Welch T J, Fricke W F, McDermott P F, et al. Multiple antimicrobial resistance in plague: An emerging public health risk [J]. PLoS One, 2007, 2(3): e309

[122] Welch T J, Evenhuis J, White D G, et al. *IncA*/C plasmid-mediated florfenicol resistance in the catfish pathogen *Edwardsiellaictaluri* [J]. Antimicrobial Agents and Chemotherapy, 2009, 53(2): 845-846 ◆