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专论与综述

养殖环境中抗生素抗性基因的研究进展

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摘　要：抗性基因在环境中的垂直及水平传播，致使抗生素耐药性成为危及人类和动物生命健康的全球性问题。动物源食品是中国美食不可或缺之物，而由于抗生素超用与滥用等行为让公众不得不关注动物源食品源头——养殖场的抗生素抗性基因环境安全问题。本文综述了养殖环境中抗生素抗性基因的研究进展，分析了养殖环境中抗生素抗性基因产生原因、传播途径以及影响因素，介绍了现有风险评估方法和控制技术，并对今后养殖环境中抗生素抗性基因的控制策略、技术及研究方向提出了建议。

关键词：养殖环境，抗生素抗性基因，传播途径，风险评价，控制技术

Antibiotic resistance genes in livestock and aquaculture environment: a review

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Abstract: The vertical and horizontal transmission of resistance genes in the environment makes antibiotic resistance as a global problem threatening human and animal health. Animal food is an indispensable part of human diet. Due to the overuse and abuse of antibiotics, antibiotic resistance genes in animal farms should be concerned. In this paper, the source, transmission routes and influencing factors of antibiotic resistance genes in animal farms, as well as risk assessment and control techniques are described, and suggestions on the future direction of researches on antibiotic resistance genes are proposed.

Keywords: Livestock and aquaculture environment, Antibiotics resistance genes, Transmission routes, Risk assessment, Control techniques

随着人们对健康问题重视的提高，食品安全问题也备受关注。动物源食品消费迅速增加[1]，兽用抗生素的使用量也因此会在未来呈增长趋势[2]。为实现畜牧养殖业绿色可持续发展，我国政府针对抗生素滥用和乱用问题出台了一系列政策，包括 2016 年 8 月 5 日，国家卫生计生委、发展改革委

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等 14 个部门联合印发了《遏制细菌耐药国家行动计划(2016−2020 年)》(http://www.gov.cn/xinwen/2016-08/25/content_5102348.htm)。2020 年 4 月 1 日，中国农业农村部又发布了《农业农村部办公厅关于实施 2020 年水产绿色健康养殖“五大行动”的通知》(http://www.yyj.moa.gov.cn/gzdt/202004/t20200401_6340570.htm)。但由于抗生素作为一种饲料添加剂，能预防和治疗动物疾病、促进动物生长、缩短出栏时间，甚至直接混合在饲料中，因此，在实际农业养殖生产过程中管控抗生素使用的工作仍然任重道远，从养殖过程产生并排放到环境中的抗生素抗性基因问题需要持续关注与研究。

抗生素除了本身是一种化学污染，也作为一种环境选择因子加速抗生素抗性基因(antibiotic resistance genes，ARGs)和耐药菌(antibiotic resistance bacteria，ARB)形成[3]。对于养殖环境来说，混杂着 ARGs 和 ARB 的动物排泄物和废弃物是污染养殖场及周边环境的主要污染源。ARGs 通过垂直与水平转移(horizontal gene transfer，HGT)在环境、动物、人体循环传播，最终危害人类健康[4]。近期，有报道称在 80%儿童尿液中都检出兽用抗生素[5]。蓄积于人体的抗生素会致使器官发生变态反应、免疫抑制等病变[6]。更严重的问题是，随着抗生素的投加使用，养殖环境中的 ARB 呈现向多重耐药菌发展的趋势[7-8]。这不仅意味着动物细菌性疾病治疗难度加大，更预示着当人类遭受 ARB 侵袭后，体内微生物群落会发生抗性改变，从而导致其他疾病治疗方案受限的后果。

2020 年的“新冠”肺炎病毒提示我们应对动物源食品安全问题要投入更多关注，而抗性基因污染所造成的抗生素失效问题，可能增加养殖生产和人类环境中疫情控制的难度。因此，本文阐述了养殖环境抗生素抗性基因的传播途径及影响因素，期望通过该部分内容的梳理，对削弱或阻断抗生素抗性基因在环境与人体间的传播给予启发，并根据所整理的风险现状、控制削减技术及其效果，提出今后养殖环境中抗生素抗性基因控制削减研究方向的建议。

1 养殖环境中抗生素抗性基因的产生、传播及影响因素

1.1 产生与传播

中国是农业和畜牧业大国，每年投用于养殖业的抗生素高达年总产量的 46.1%[9]。对于兽医及饲养员来说，养殖环境的复杂性致使难以针对某只动物做精准用药测试。因此，多数情况下，由于不了解或不讲究休药期，抗生素使用的量与种类处于“超需”状态。长此以往，抗生素非但没有在时间作用下降解，反而逐步累积，迫使动物体及体内微生物产生 ARGs，并进入环境，扩大污染面。

ARGs 之所以广泛分布于不同环境，微生物的介导起了重要作用。ARGs 可以随着微生物在不同环境介质中和介质之间迁移，甚至在特定条件下实现微生物之间的水平迁移。当 ARGs 或者 ARB 进入环境后，不但能以细胞分裂等垂直基因转移方式在亲代间进行传递[10]，还能通过接合[11]、转化、转导等方式在不同菌种间进行水平转移[12]。在养殖过程中，有些国家习惯于用清水冲洗动物排泄物，并将粪水用于肥料施用，或者用作某些水生植物饲料。这在一定程度上是一种环保行为，但不可忽略的是，这种行为同时也提供了 ARGs 与 ARB 进入施用土壤和水体的机会，最终影响人体健康，传播途径见图 1。

当粪便和底泥作为肥料施用于农田时，其中残留的抗生素和裹挟的 ARGs 同样会对农作物及其内生细菌产生影响，如抑制农作物发芽、缩短根长与株高及提高耐药细菌比例等[13-14]。长期使用动物粪便作为有机肥料，一方面会对土壤微生物群落结构产生影响，改变群落功能；另一方面也会使土壤中的 ARGs 和移动元件丰度显著提升，诱导 ARB 的产生与进化[15]。富含抗生素抗性基因的养殖废水及相关水体经挥发，最终随降雨回归大地，也成为了养殖场周边环境抗生素抗性基因检出浓度随季节性变化的主要原因之一[16]。此外，当人体暴

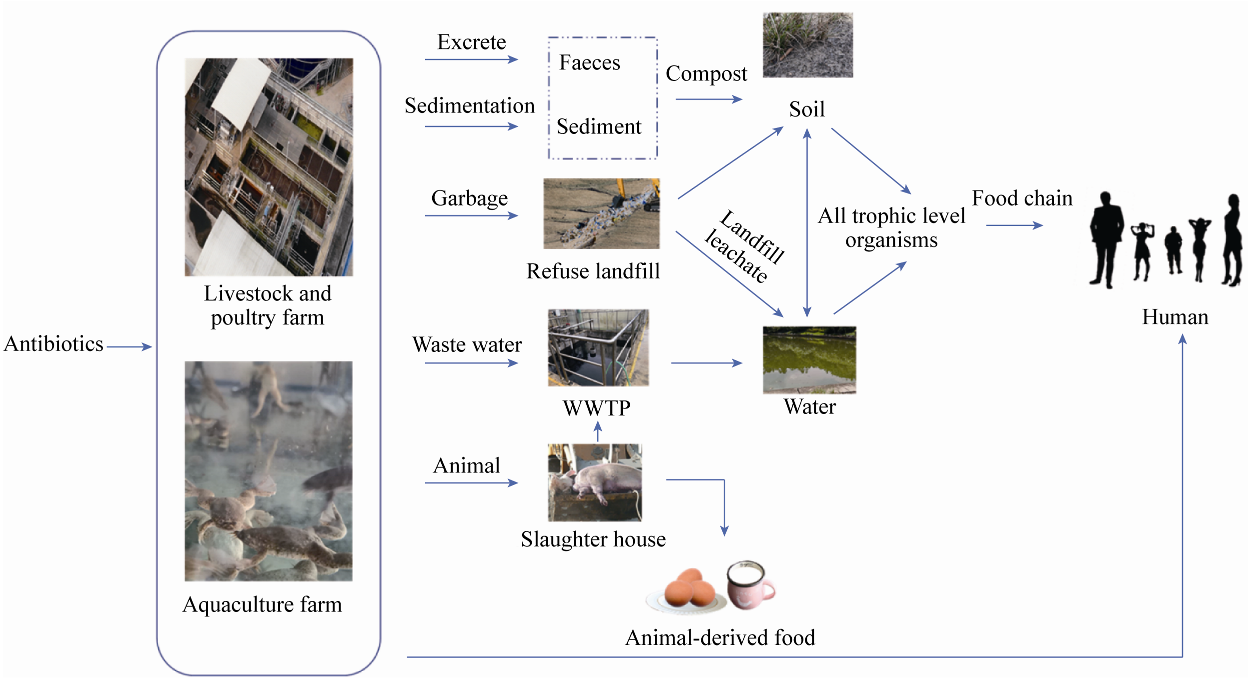

图 1　兽用抗生素进入人体示意图

Figure 1　Schematic diagram of veterinary antibiotics entering the human body

露于高风险养殖环境中时，人类肠道微生物菌群和耐药性将随环境改变并导致其功能重塑[17]。食物链很可能是 ARB 和 ARGs 通过日常食物摄入向人类宿主传播的主要途径。当人们食用动物体及其产品时，残留其中的 ARGs 和 ARB 与肠道菌群接触后，对菌群的生态及人体健康均会产生不利影响[18]。总的来说，人类活动大幅度地改变了微生物的生物地理学，致使养殖环境产生的抗生素残留和 ARGs 通过水体和土壤污染各级营养物，最终随食品供应链或其他途径传播至全球，危害地球上所有生物体的健康[19]。

1.2　影响因素

影响养殖环境抗生素残留及 ARGs 迁移性的主要因素大致可分为三类。

第一类为季节和降雨量等自然因素。如我国重要的水产养殖基地——鄱阳湖会由于旱季水体表面积缩小导致局域抗生素残留浓度增高，ARGs 富集；同时，旱季水体中诱导 ARGs 发生水平迁移的污染物浓度也升高[20]。

第二类为养殖场周边功能区划分和养殖废弃物处理方式等人为因素。当养殖场与工业区相邻时，工业区污水与养殖场废物共同作用于附近土壤或水域，来自工业区的重金属离子可通过协同作用影响养殖环境 ARGs 的表达与增殖[21-23]。当使用不同工艺处理养殖废弃物时，对抗性基因丰度和多样性的影响也随之改变。例如在处理动物粪便时，好氧堆肥过程可显著降低堆肥中 ARGs 的丰度和多样性[24]，而厌氧消化时，动物粪便中的某些 ARGs 丰度反而有所上升[25]。

第三类为养殖类型和养殖方式等养殖场自身因素。研究证明，养猪场与养鸡场的 ARGs 丰度与多样性高于养牛场[26]。有抗养殖会导致抗生素累积于鸡的腿肌、胸肌和肝脏，舍养的残留状况相对放养表现得更为严重[27]。

综上所述，影响养殖环境中抗生素残留持久性及 ARGs 传播的因素十分复杂。正因为如此，全面分析养殖环境中 ARGs 的影响因素，对于合理设计实验和科学研究 ARB 耐药变化趋势非常重要。

2　养殖环境中抗生素抗性基因的风险评价方法及现状分析

动物养殖时使用的抗生素,部分会随食物链传递至人类。在对比不同饮食习惯人群的肠道菌群时发现，*sul2* 和 *strB* 在杂食和肉食人群的肠道中检出率更高,这意味着该类基因从动物源食品获得的可能性要高于蔬果[28]。特别是屠宰场废水会携带大量的耐药性人畜共患菌排入市政污水,处理不当将增大人体接触耐药性人畜共患菌的几率[29]。因此,亟需研究出一套适用于评价养殖环境抗生素残留及 ARGs 风险的合理方法。目前，专用于抗生素及其衍生问题的标准和方法尚未形成,关于养殖环境的抗生素风险评价仍采用污染物风险评价方法,即：概率生态风险法(probabilistic ecological risk assessment，PERS)、物种敏感性分析法(species sensitivity distribution，SSD)[30]和风险商值法(risk quotient，RQ)[31]。其中，风险商值法由于参数少和计算简单的优点常应用于抗生素风险评价。除此之外，Liang 等[32]结合宏基因组和流式细胞分析，对潜在的致病性抗生素耐药菌(pathogenic antibiotic resistant bacteria，PARB)进行识别和定量,提出了利用 PARB 丰度评估环境耐药菌风险的新思路。

表 1 列举了我国部分地区养殖相关环境因素中的风险状况。表 1 及其他相关文献表明，目前养殖环境中抗生素及 ARGs 的流出对周边环境造成的风险等级大多为中低风险。从抗生素种类来看,四环类、磺胺类、大环内酯以及喹诺酮类由于应用广泛,在养殖环境抗生素抗性基因风险综合评价时贡献占比较大。养殖环境中抗生素种类及主要亚型也与其他环境检出的不同，Fan 等[38]在对比城市、工业和混合污水中的抗性基因主要亚型时发现，3 种污水的 ARGs 主要亚型相似，如 *tetA*、*tetG*、*tetH* 和 *tetJ* 是四环类的主要亚型，而禽畜养殖场中的核糖体保护蛋白类抗性基因(*tetM*、*tetQ*、*tetW*、*tetO*)的丰度要高于外排泵抗性基因和酶蛋白修饰抗性基因[39]。因此，在处理养殖废水时，可优先考虑去除占比较大的核糖体保护类抗性基因。从作用的环境介质来看,由于水体的流动性会使进入其中的抗生素和抗性基因浓度降低,但水体内浓度均一,而进入土壤的抗生素和抗性基因将呈现由表及里浓度逐步递减的趋势。因此，动物粪便或养殖废

表 1　我国部分地区养殖相关环境因素中的风险状况
Table 1　Risk profile of culture-related environmental factors throughout the country

地区 Region	样本 Sample	抗生素种类 Type of antibiotics	风险评估 Risk assessment	参考文献 References
Beijing	Pig excrement	TCs	Concentration range: 0.48−29.2 mg/kg, 27% above the EU soil ecological safety line for antibiotics	[33]
Zhejiang	Organic fertilizer	SAs, QNs, TCs	Detection rate: TCs>QNs>SAs The detection rate of doxycycline was the highest (52%), with a concentration of 0.2−71.0 mg/kg. The risks are high	[34]
Jiangsu	Water and sediment of *Procambarus clarkia* aquaculture environments	MCs, TCs, QNs, SAs	There is little risk to plankton growth, but a high ecological risk to algae	[35]
Chongqing	Pig excrement	TCs	OTC, TC and CTC risk ratios: high: 0, 0, 7%, medium: 53%, 13%, 70%, low: 47%, 87%, 23% RQ: CTC>OTC>TC	[36]
Southern aquaculture	Water	QNs, SAs, TCs, MCs and others	Most antibiotics do not have a single ecological risk, but the combined toxicity of antibiotics in aquaculture areas presents a moderate risk	[37]

注：TCs：四环类抗生素；SAs：磺胺类抗生素；QNs：喹诺酮类抗生素；MCs：大环内酯类抗生素；RQ：风险商值.
Note: TCs: Tetracyclic antibiotics; SAs: Sulfanilamide antibiotics; QNs: Quinolones; MCs: Macrolide antibiotics: RQ: Risk quotient value.

水施于农田后，将对作物构成很高的潜在风险[40]。但部分抗生素在低浓度时反而促进水生植物生长[41]，存在生态失调风险。由上可知，养殖环境中抗生素抗性基因进入水体环境具有低浓度、范围广等特点，而进入土壤环境时，则具有表层高浓度特点。从地理位置及发展状况来看，由于我国经济发展及养殖模式的差异，抗生素抗性基因污染呈现出东部地区高于西部、沿海沿江地区高于内陆的现象。此外，目前大多采用累加法来评价多种抗生素的风险状况，但累加法忽略了抗生素之间、降解产物之间的毒性相互作用，因此对养殖环境中抗生素抗性基因的风险存在低估。

3 养殖环境中抗生素抗性基因的控制策略及削减技术

3.1 控制策略

针对污染控制手段通常分为源头预防、过程控制和末端治理三方面，而其中最具成效的就是源头预防。抗生素的使用可以为养殖户们带来一定的增产作用，但切不可违规盲目使用抗生素，造成食品安全和环境污染问题。对此，美国食品和药品管理局(Food and Drug Administration，FDA)收集抗菌药物的销售和分销数据以确保医用抗菌药物的合理应用[42]，中国则在 2016 年、2017 年连续两年发布《抗生素合理使用宣传手册》[43-44]。在养殖过程中，减少如微塑料、重金属等可与抗生素及 ARGs 有共选择作用污染物的接触，以避免共选作用下多重耐药致病菌的形成与传播，也是从源头阻断抗生素抗性基因的思路[45]。除此之外，首先应对休药期和物种特性进行相关了解，根据不同物种和不同环境条件，给予抗生素在动物体内吸收预留充分的时间，避免过度用药、浪费资金。如鸡、鸭等动物由于消化道短，导致所服抗生素吸收量少，粪便中抗生素残留多，就需要额外注意该种粪肥带来的环境风险；其次，可考虑使用其他治疗方案替代抗生素治疗，目前主要替代物包括植物源提取物、微生态制剂、抗菌肽等，现有方法见表 2。植物提取物大多具有高效杀菌、抑菌的作用，正确使用不但可以调节与改善动物肠道能力，促使肠道内微生物构成健康发展，还能提升动物消化能力与产物能力。中药成分作为植物提取物的重要代表，其功效已在中国源远流长的历史中证实，而且经过现代技术的改进，得到了进一步的提高。相比见效迅速的西药来说，中药具有低毒性、低环境影响的特点，而且能在治病过程中逐步调理生物体身体素质，起到治疗、预防的双功效。微生态制剂应用于陆上动物时常以投喂方式进入动物肠道，使制剂中益生菌与肠道益生菌共同发挥作用，建立更平衡的微生物菌落

表 2 现有抗生素替代物及其效果

Table 2 Existing antibiotic substitutes and their effects

替代物 Substitute	主要成分 Main ingredients	功能主治 Function of the attending	参考文献 References
Plant derived extract	Genipin	Within 24 hours, the replication of White spot syndrome virus in crayfish and shrimp was inhibited with only 50 mg/kg genipin at a 99% inhibition rate	[46]
Plant derived extract	Ginger essential oil	It can be used for the lipid peroxidation reaction of the reproductive cells of quail, promoting the improvement of the reproductive ability, and has no adverse effect on the growth performance	[47]
Microecological preparation	Fermented Chinese herb	The weight and weight gain rate of broiler chickens were significantly increased, the survival rate was increased to 99.89%±5.67%, and the incidence rate was reduced to 1.14%±0.19%	[48]
Antimicrobial peptides	Recombinant plectasin	Recombinant plectasin stimulated up-regulation of *CLDN1* and *ZO-1* genes, improving intestinal function, epigenetic digestibility of nutrients, and positively altered intestinal morphology and enzyme activity	[49]
Bacteriophage	Bacteriophage	It is suitable for intensive farming and can significantly reduce pathogens	[50]
Engineered strain	*Escherichia coli* ereA	The level of erythromycin in faecal seed of the experimental group was reduced by 83.13% compared with the control group	[51]

构成，以提高动物体抗病能力。应用于水厂养殖业时，解决了需要通过持续投加化学药品或换水来维持水质的问题，利用微生物的降解能力使水环境中有机物或食物残渣被逐步降解，改善水产动物的体外环境。同时，某些细菌如硝化细菌可产生无害于水生动物的硝酸氮，从而减少其他致病因子带来的毒害性[52]。抗菌肽具有广谱抗菌性和不易产生ARB 等优点，进入动物肠道后可改变其组织形态，在促进消化吸收功能的同时达到调节肠道菌、杀灭有害菌的目的，以提高生物体抵抗力与机体活性，改善产物性能与品质。

在过程控制阶段可分为两方面。一方面是微观控制手段。随着同位素标记与荧光标记等技术的成熟，通过标记细菌、质粒或其他遗传元件等途径设计接合条件，以此得到抗生素抗性传播的可视化过程，是目前研究重点方向之一。目前常用的接合方法包括滤膜接合法[53-54]和微流控芯片接合法[55-56]。传统的滤膜接合法适用于实验室测试，但计算接合频率时所用筛选板数量多，不适用于一次性多抗性测试，而新兴的微流控芯片接合法采用注射泵不断供给营养液，解除了因营养限制造成的接合界限，更适用于模拟环境情况。这种方法无疑是通过探究传播途径以获得阻断 ARGs 传播的有效手段，只是目前仍需进一步探索。另一方面是宏观控制手段，建立更全面的监测网站以控制养殖环境中的抗生素及 ARGs 随污染物、工作人员、动物产品甚至苍蝇传递至外界。

3.2 削减技术

针对抗生素抗性基因的削减技术可分为两类。第一类为优化型，即对已应用于实际养殖废弃物处理的工艺进行抗生素抗性基因去除效果评估，将多种工艺进行有机结合，达到既可保证常规污染物的处理效果，又可对抗生素残留与 ARGs 有较好去除性能的目的。现有工艺技术可分为物理法、化学法和微生物法[57]。物理法常利用添加物的吸附作用，将单一或多个组分富集于吸附物表面再去除。常用吸附剂有生物炭、活性炭、火山渣等，效果受吸附剂种类影响。其缺点在于并未使抗生素或抗性基因失效，后续还存在吸附剂处理和解析的问题。化学法中的高级氧化对抗生素分解能力强，而且具有明显去除效果。微生物降解法则相对经济实惠，能重复利用，还可根据污染物特性调整微生物构成以达到不同降解效果。近期研究发现，即使剩余污泥中土霉素含量高达 40 000 mg/kg，嗜热厌氧消化过程仍可有效地降低 ARGs 总丰度[58]。在畜禽污水处理过程中，残留的兽用抗生素一般在吸附与生物降解过程的去除率较高[59]。值得注意的是，经过微生物法与化学法处理后的抗生素降解中间产物可能因毒性增强而使得环境风险增大。因此，基于现有技术的应用效果及养殖废水的“三高”特性，当废水中抗生素浓度较低时，采用臭氧处理即可获得较好的抗生素及抗性基因去除效果，相对其他生物处理工艺，膜生物反应器在去除 ARGs 方面表现更为优良。当处理复合抗生素污染或高浓度抗生素污染废水时，应结合各方法优点进行耦合，保证去除效果。如处理含高浓度难降解抗生素的有机废水时，以水热法作为预处理，可达到良好的抗生素及抗菌活性去除效果，同时提高甲烷产量[60]。因此，多法联用也将是后续的研究重点。第二类为创新型，即对某工艺投加新型材料或技术，在原有基础上新增或放大抗生素抗性基因处理效果。如改性后的石墨毡通过电氧化法对持续存在的土霉素有良好的降解效果[61]，光催化材料对土霉素降解效果同样优良[62]。以水、陆养殖废水处理为例，现有技术及效果见表 3。

总而言之，目前削减技术大多只对单一或同类抗生素有较好的效果，因此，需要针对不同类型的养殖环境废弃物处理工艺所能去除抗生素和抗性基因的效果作出评估，在尝试不同组合效果的同时利用新材料、新技术不断进行尝试。在选用削减工艺时，还需对污染特性、效果及预算进行综合考量。

表 3 现有技术对水、陆养殖废水中抗生素和抗性基因的削减控制效果

Table 3 Reduction control of antibiotic and resistance genes in water and land aquaculture wastewater by prior art

类型 Type	削减控制技术 Reduction control technique	关键参数 Key parameter	效果 Effect	参考文献 References
Aquaculture wastewater	Algal biofilm membrane photobioreactor (BF-MPBR)	Algal biomass productivity, total microalgae, HRT	During the 1−2 days of operation, the contents of sulfadiazine (SDZ), sulfamethoxazine (SMZ) and sulfamethoxazole (SMX) were reduced by 61.0%−79.2%, 50.0%−76.7% and 60.8%−82.1%, respectively. The removal efficiency of inorganic nitrogen and dissolved inorganic phosphorus was 91.0%−99.6% and 92.1%−98.4%, respectively	[63]
Mariculture wastewater	CuO/ZnO composite photocatalyst	CuO/ZnO dosage, H_2O_2 concentration, reaction time	The maximum removal rate of tetracycline hydrochloride can be reached at 4 h, and the average removal rate can reach 93.01%	[64]
Swine wastewater	Pomelo peel derived biochar	Temperature, surface area, pore volume	Considering the low concentration of the TCs in the wastewater, the removal rate of TCs will more than 80%. The material is effective, cheap and environmentally friendly	[65]
Swine wastewater	Biological aerated filter system (combination of indoor aerobic and anaerobic culture)	HRT	The removal rate of nine antibiotics such as sulfamethoxazine, norfloxacin and lincomycin was good, and the removal rate of pollutants in conventional wastewater reached 82%	[66]
Swine wastewater	Nanofiltration and reverse osmosis processes	Membrane aperture, osmotic pressure	Compared to raw sewage, the absolute gene copy number of ARGs efficiently decreased 4.98–9.52 logs, the common nitrogen and phosphorus components in the water were also reduced	[67]
Livestock and poultry waste water	UV/H_2O_2 combined oxidation process	Initial pH value, H_2O_2 dosage, reaction time	After optimizing the parameters, the removal rate of five types sulfanilamide antibiotics can reach more than 95%	[68]

4 总结与展望

食品安全与人体健康息息相关，尽管目前养殖环境所带来的抗生素抗性基因污染属于中低风险，但我们仍需防微杜渐。理应减少乱用、滥用抗生素行为，然而仅凭单纯减少抗生素的使用并不能使抗生素抗性逆转[69]，而且单一处理工艺对养殖废水中抗生素抗性基因的去除效果不尽人意。因此，解决养殖环境抗生素抗性基因问题需要另辟蹊径。养殖环境中抗生素抗性基因具有基值大、种类多等特点，导致 ARB 易向多重耐药方向发展，而且随季节或其他因素动态变化。针对这种状况，对今后研究方向提出以下建议：(1) 明确养殖环境中影响抗性传递的主要菌属，针对菌属特点进行杀灭处理，减少抗性基因传递可能性；(2) 探寻阻断抗生素抗性基因改变敏感菌的方法，延缓或阻止 ARB 向多重耐药菌的发展；(3) 结合养殖废水“三高”特点，研发针对养殖废水中的多种抗生素抗性基因联合处理技术。

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