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Review 综 述

细菌抵抗消毒剂及其对抗生素共耐药

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摘　要：消毒剂是一种可杀灭物体表面、器材设备、皮肤、空气和水源等传播媒介上携带的病原微生物的有机分子。它在体外能杀灭病原微生物，切断其传播途径，进而达到控制污染的目的，在生命安全防控中起着重要的作用。但是不合理地使用消毒剂导致细菌对消毒剂产生耐药。消毒剂耐药基因在不同种属间的水平转移加剧其传播风险，使消毒剂耐药情况进一步恶化。更令人担忧的是，细菌对消毒剂的耐药可能会导致对抗生素产生共耐药，给公共安全带来巨大的威胁。但目前为止，对消毒剂耐药以及共耐药的认识还不够全面。本文总结了关于细菌对消毒剂耐药的研究报道，对消毒剂的作用机制、细菌对消毒剂的耐药机制进行了论述，另外针对消毒剂耐药基因的传播以及细菌对消毒剂和抗生素的共耐药进行了综述，为减少消毒剂耐药性的产生和制定合理的消毒剂使用规范奠定基础。

关键词：消毒剂；消毒剂耐药机制；消毒剂耐药基因；传播；共耐药

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Resistance of bacteria to disinfectants and co-resistance of disinfectant-resistant bacteria to antibiotics

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Abstract: Disinfectants are organic molecules that kill pathogenic microorganisms on object surface, equipment, and skin, in the air and water, and carried by other vectors. They can kill pathogenic microorganisms *in vitro* and cut off their transmission routes to achieve contamination control, playing a role in ensuring life safety. However, the irrational use of disinfectants leads to resistance of bacteria to disinfectants. Horizontal transfer of disinfectant resistance genes between different species exacerbates the risk of transmission, aggravating resistance to disinfectants. Moreover, bacterial resistance to disinfectants may lead to co-resistance to antibiotics, posing a huge threat to public safety. However, the knowledge about resistance to disinfectants and co-resistance to disinfectants and antibiotics is limited. We review the research reports on the resistance of bacteria to disinfectants, introduce the mechanisms of disinfectants and the mechanisms of bacterial resistance to disinfectants, and expound the spread of disinfectant resistance genes and the co-resistance of bacteria to disinfectants and antibiotics. This review lays a foundation for reducing the emergence of disinfectant resistance and formulating reasonable specifications for the use of disinfectants.

Keywords: disinfectant; mechanism of resistance to disinfectant; disinfectant resistance gene; spread; co-resistance

消毒剂(disinfectant)可通过抑制或破坏包括传播介质上的病原体生长来控制传染病的传播[1]，在医院治疗、食品加工等行业被大量地使用(图 1)。新型冠状病毒肺炎疫情发生后，消毒剂被广泛用于公共场合以及手部的消毒。含氯类、醛类、过氧化物类、胍类和季铵盐类等消毒剂是市面上常见的消毒剂。不同类型的消毒剂组成成分不同，故作用机制也不一样。

然而绝大数的使用者在使用之前没有了解和掌握正确的消毒剂使用方法，使消毒剂的不合理使用和滥用情况越来越严重。这势必会和由于抗生素的滥用和不合理使用导致的抗生素耐药性类似，产生消毒剂耐药，使消毒失败(图 1)。研究发现，粪肠球菌反复暴露于氯己定(chlorhexidine, CHX)后，其对氯己定最小抑菌浓度(minimum inhibitory concentration, MIC)持续增加[2]。另外，消毒剂耐药基因的传播更是使得耐消毒剂细菌数量得到快速增长，对生态系统构

成严重的威胁。后续研究发现细菌对消毒剂产生耐药后对部分抗生素也变得耐药。大肠埃希菌逐步暴露于亚抑菌浓度不断增加的二癸基二甲基氯化铵后，不仅对自身消毒剂的敏感性降低，且多数菌株对氯霉素产生耐药[3]。本文针对消毒剂作用机制、消毒剂耐药性机制、消毒剂耐药性的传播和细菌对消毒剂和抗生素的共耐药几个方面进行论述，对消毒剂的现状进行总结。

1 消毒剂对细菌的作用机制

不同种类消毒剂作用机制各异：过氧化物类消毒剂产生的强氧化性羟基自由基使细菌大分子物质被氧化，从而达到高效的杀菌效果[4-5]；季铵盐类、胍类消毒剂通过作用于细菌的细胞膜或细胞壁，改变细菌的渗透平衡而发挥杀菌作用[6]；醛类以及含氯消毒剂作用于细菌的蛋白质等大分子物质而使细菌死亡[7]；另外，抑制细菌生物被膜的形成也是消毒剂的作用机制之一[8]。

消毒剂的作用效果还与细菌本身的特性有关：细菌芽胞最耐药，其次是分枝杆菌，然后是细胞壁成分比较复杂的革兰阴性菌。另外环境因素(环境温度、接触表面、干扰物质)也会影响消毒剂消毒效果[9-11]。了解影响消毒剂消毒效果的各方面因素，可以提高消毒剂的消毒效率，减少耐药性的产生。否则可能导致部分细菌未被消毒剂杀灭而在选择性压力下存活，对消毒剂产生耐药。

2 细菌对消毒剂的耐药机制

消毒剂的不恰当使用是导致细菌产生消毒剂耐药性的重要原因[12]。正确地使用消毒剂可以快速杀灭细菌，细菌几乎不会通过适应或其他机制产生耐药性。但是在实际消毒过程中，待消毒物品往往会有各种有机物的残留或者其他情况导致消毒剂被稀释而未达到杀灭细菌所需浓度，处于亚致死浓度。若细菌长期暴露在亚致死浓度的消毒剂下，细菌通过各种机制来逐步适应该浓度的消毒剂，最终变成对该消毒剂产生耐药[13]。细菌主要通过靶点的改变、产生特异性酶、降低膜通透性、表达外排泵以及形成生物被膜几个方面来对消毒剂产生耐药(图 2)。其中，前 4 种机制在抗生素耐药性中也很常见，而形成生物被膜的耐药机制主要在消毒剂耐药性中报道。在实际面临消毒剂的伤害时，细菌可能会采取多种策略抵抗消毒剂。

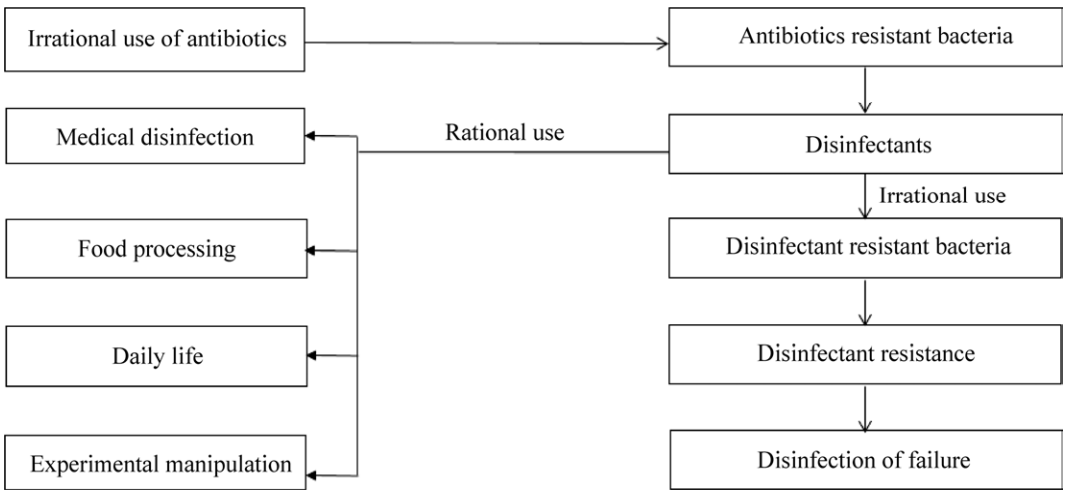

图 1 消毒剂的应用

Figure 1 Application of disinfectants.

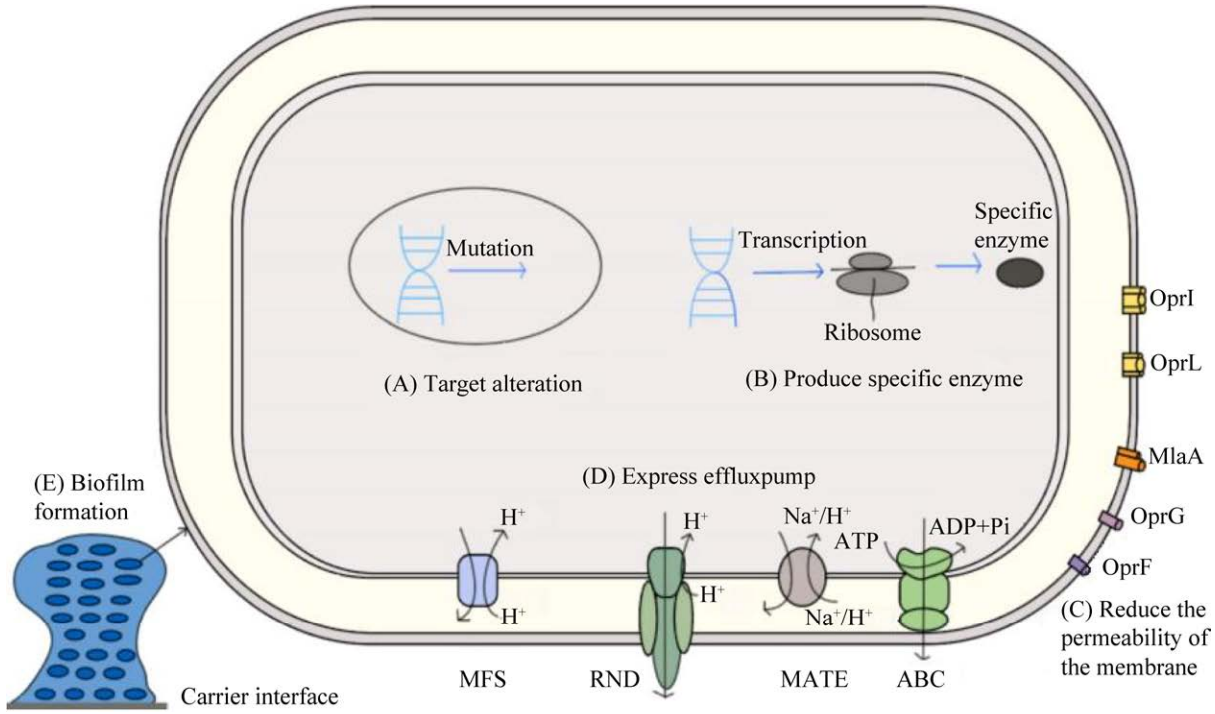

图 2　细菌对消毒剂的耐药机理

Figure 2　Mechanisms of bacterial resistance to disinfectants. A: The target of disinfectant is mutated, and the affinity of disinfectant to bacteria is decreased. B: Bacteria resist disinfectants by producing resistance-associated specific enzymes *via* transcription and translation. C: Bacteria reduce penetration of disinfectants into cells by reducing expression levels of porins and lipoproteins in the outer membrane of cells. OprG and OprF are outer membrane porins, OprL and OprI and MlaA are outer membrane lipoproteins. D: Bacteria pump disinfectants out of the cell by enhancing the expression levels of efflux pumps, such as ABC, MFS, RND, MATE family. E: Bacteria are protected from adverse environments and disinfectants by forming biofilms on attached carrier surfaces.

2.1　靶点的改变

细菌在消毒剂结合部位发生突变或修饰，降低与消毒剂的亲和力，从而减少与消毒剂的结合(图 2A)[14]。靶点改变的耐药机制在抗生素耐药性中更常见，在消毒剂耐药性中较少见。目前对导致消毒剂耐药的靶点变化的研究主要集中在三氯生(triclosan, TCS)。三氯生可以与大肠埃希菌中编码脂肪酸合成的烯酰基-酰基载体蛋白还原酶的 *fabI* 基因紧密结合。当使用低浓度的三氯生时，*fabI* 基因发生突变，导致大肠埃希菌对三氯生产生耐药[15]。

2.2　产生特异性酶

细菌暴露在消毒剂下可通过合成针对该消毒剂的特异性酶来减少消毒剂的伤害，降低其杀菌效果(图 2B)。研究发现，A 组链球菌合成的 NoxA 和 AphC 氧化酶可以分解过氧化氢(hydrogen peroxide, HO)[16]。铜绿假单胞菌暴露在次氯酸(hypochlorous acid, HClO)下，编码烷基氢过氧化物酶 AphD 蛋白的 *rcsA* 基因表达水平增加，合成相应的酶来降解次氯酸钠(sodium hypochlorite, SHY)[17]；另一方面，细菌也可能产生具有特定功能的酶来调节自身，从而提高对消毒剂的耐药性[18]。

2.3　降低细胞膜通透性

一些细菌通过降低细胞膜通透性来减少甚至阻止消毒剂进入细胞内，从而对消毒剂产生耐药。这类细菌的消毒剂耐药性主要取决于细胞外

膜[19]。一方面，与细胞膜稳定性和完整性相关的膜蛋白、脂蛋白的表达增加可减少消毒剂进入细菌内。研究发现，荧光假单胞菌经过戊二醛诱导后，*secA*、*secB* 等基因转录水平增加，使蛋白质转运系统更稳定[20]；另一方面，减少一些膜蛋白的功能表达可降低细菌对消毒剂的敏感性。铜绿假单胞菌通过减少外膜孔蛋白 OprG 和 OprF 和脂蛋白 OprL 和 OprI 的表达水平，减少苯扎氯铵(benzalkonium chloride, BAC)的渗透[19]。还有研究发现大肠埃希菌通过减少外膜脂蛋白 MlaA 的转录水平来减少氯己定进入细胞内，对氯己定产生耐药(图 2C)[21]。

2.4 外排泵系统

一些细菌在消毒剂压力下，通过外排泵外排作用将消毒剂快速、高效地排出，从而产生耐药。外排泵可分为 5 个膜蛋白家族，包括 ATP 结合盒家族(ATP binding cassette, ABC)，主要易化家族(major facilitator superfamily, MFS)，多药与毒物外排家族(multidrug and toxin extrusion, MATE)，小多药耐药家族(small multidrug resistance, SMR)和耐药结节分化家族(resistance nodulation and cell division, RND) (图 2D)。表 1 列出了不同外排家族的具体种类以及涉及到的细菌和消毒剂。其中，RND 家族常存在于革兰阴性菌中，而 MFS 家族多见于革兰阳性菌中。一般来说，多个外排泵共同发挥作用，将消毒剂排出。外排泵的过表达可以独立或与其他耐药机制共同抵抗消毒剂的伤害。

2.5 形成生物被膜

细菌在其接触表面产生的生物被膜可以减少消毒剂的进入，起到一个抵抗恶劣环境的屏障作用，为被膜内细菌的生长提供一个稳定的环境(图 2E)。大肠埃希菌生物被膜内的细菌对次氯酸钠具有更强的抵抗能力[33]。研究发现，亚致死浓度的消毒剂处理可刺激某些细菌形成生物被膜。经过亚致死浓度的乙醇和氯胺联合处理后，金黄色葡萄球菌的黏附素基因表达增加，生物被膜形成更完整[34]。另外，混合物种形成的生物被膜比单一物种形成的生物被膜具有更强的抵抗消毒剂能力[35]。

表 1 细菌对消毒剂的主要外排泵

Table 1 Major efflux pumps for disinfectants by bacteria

Family	Efflux pump	Bacteria	Disinfectant	Reference
ABC	PatA, PatB	*Streptococcus pneumoniae*	Acriflavine	[22]
MFS	NorA	*Staphylococcus aureus*	Benzalkonium chloride, chlorhexidine	[23]
	Lde	*Listeria monocytogenes*	Ethidium bromid	[24]
	MdrL	*Listeria monocytogenes*	Benzalkonium chloride	[25]
	QacA, QacB	*Staphylococcus aureus*	Quaternary ammonium compound	[26]
MATE	MdtK	*Escherichia coli*	Quaternary ammonium compound	[27]
SMR	QacC, QacG, QacH, QacJ	*Staphylococcus aureus*	Benzalkonium chloride	[26]
RND	AcrAB-TolC	*Escherichia coli*	Chlorhexidine	[28]
	MexAB-OprM	*Pseudomonas aeruginosa*	Chlorhexidine	[29]
	CmeABC	*Campylobacter*	Chlorhexidine, benzalkonium chloride	[30]
	OqxAB	*Klebsiella pneumoniae*	Benzalkonium chloride	[31]
	Tri ABC	*Pseudomonas aeruginosa*	Triclosan	[32]

3 消毒剂耐药基因的传播

获得性消毒剂耐药基因根据基因所处位置可将其分为两种：一种位于染色体上，例如，*sugE(c)*、*emrE*、*ydgE/ydgF* 和 *mdfA* 基因位于细菌染色体上，赋予细菌对季铵盐类消毒剂产生耐药；另一种是在可移动遗传元件中。一般来说，

染色体介导的耐药基因通常进行垂直传播。而可移动遗传元件上的耐药基因可通过水平转移传播耐药性，扩大耐药细菌的数量和范围。基因的水平传播(horizontal gene transfer, HGT)是一个重要的提高消毒剂耐药性的贡献者，通过水平转移获得抗消毒剂基因是较不敏感细菌对消毒剂产生耐药的主要途径[36]。消毒剂耐药基因的传播，一方面会降低消毒剂的消毒效率；另一方面，这种基因污染物可能对生态环境和人类健康构成严重威胁，给公共卫生安全和医院治疗带来巨大的困难和挑战。

可移动遗传元件(mobile genetic elements, MGE)是细菌传播消毒剂耐药性的重要载体。消毒剂耐药基因的转移和广泛流行往往是由可移动遗传元件的运动引起的，进而使消毒剂耐药细菌的数量进一步增加。可移动遗传元件包括质粒、整合子、转座子和插入序列等。这些可移动遗传元件之间的相互作用可能是消毒剂耐药性迅速出现的原因之一。位于细菌质粒上的消毒剂耐药基因与细菌对消毒剂敏感性降低相关。*qac*基因在导致细菌消毒剂耐药的消毒剂耐药基因的研究中更常被报道，这一类基因主要介导细菌对季铵盐类消毒剂产生耐药。其中，*qacA*、*qacB*和*qacC*基因可介导金黄色葡萄球菌对消毒剂产生耐药，而*qacE*、*qacEΔ1*、*qacF*和*qacG*基因主要与革兰阴性菌对季铵盐类的耐药性有关。*qacA*和*qacB*基因位于大质粒上，而*qacG*、*qacH*和*qacJ*基因位于小于3 kb小质粒上，在小质粒上发现的耐药基因常见于基因盒中。前者通常编码MFS家族，后者主要编码SMR外排家族[37]。肺炎克雷伯菌中发现的*qacΔE*、*qacE*等耐药基因与其对戊二醛等消毒剂的耐药性有关，这些基因存在于质粒上并且能够整合至染色体上[38]。*sugE(p)*基因通常位于沙门菌IncA/C多药耐药质粒上，介导对季铵盐类消毒剂的外排作用[39]。较大的转座子通常携带一个或多个耐药基因。单核细胞增生李斯特菌中位于转座子Tn6188上编码SMR外排家族的*qacH*基因赋予其对季铵盐类消毒剂的低水平耐药性[40]。

消毒剂耐药基因通常借助MGE在不同菌株和物种之间水平转移，其中由接合质粒介导的水平传播在耐药性传播中最常见[36]。由质粒介导的消毒剂耐药基因不但可以在同物种的不同菌株之间，甚至可以在不同细菌物种之间传播。研究发现，在季铵盐类消毒剂存在的情况下，携带编码SMR家族外排泵的苯扎氯铵耐药基因*bcrABC*的质粒可以通过接合在不同致病性和非致病性单核细胞增生李斯特菌之间进行转移[24,40-41]。耐甲氧西林金黄色葡萄球菌中携带*qacA*的接合质粒可以接合转移至大肠埃希菌内，导致大肠埃希菌对氯己定的敏感性降低[42]。耐药基因可以通过单位转座子在同一细菌中从染色体转座到一个质粒中，或从一个质粒转座到另一个质粒中[36]。质粒中的耐药基因可以以基因盒的形式被切除，并在不同的整合子之间移动[43]。携带耐药基因的基因盒也可以再次被质粒捕获。从供体DNA中提取的接合质粒和环状共轭转座子都可以通过接合转移将耐药基因转移至受体中[41-43]。然而，消毒剂耐药基因能否通过更简单的转化或者通过噬菌体进行转导使受体获得耐药性尚不清楚，这可能是未来需重点关注的。此外，对编码消毒剂耐药性的可移动遗传元件结构的信息了解也有限。

4 消毒剂和抗生素共耐药

细菌对消毒剂和抗生素的共耐药是指细菌长期在各种原因导致的亚抑制或者亚致死浓度的消毒剂作用下，对消毒剂本身以及其他抗生素的敏感性均发生了变化。消毒剂的滥用和不合理使用不仅导致细菌对消毒剂耐药，而且当细菌存

在抗生素和消毒剂共同的耐药机制或本身携带某些耐药基因时，细菌就可以选择对抗生素的耐药性[44]，导致细菌对部分抗生素产生共耐药，使细菌的耐药现状进一步恶化和难以控制，产生比单纯的耐药菌更大的危害，给一些细菌性疾病的治疗带来更大的挑战和困难。但是目前对于共耐药的研究还较少，机制方面也尚未深入。

4.1 消毒剂和抗生素共耐药现象

研究发现，细菌对消毒剂和抗生素的共耐药现象主要发生在季铵盐类消毒剂、阳离子活性剂以及次氯酸钠中。另外，肠杆菌科中的细菌共耐药现象较为突出。有报道发现沙门菌在暴露于亚抑制浓度的季铵盐类等 4 种消毒剂期间选择了抗生素耐药突变体，且发现部分突变体对喹诺酮类抗菌药物和三氯生均高度耐药[45]。将单核细胞增生李斯特菌和沙门菌等食源性病原菌逐步暴露于亚抑菌浓度不断增加的二癸基二甲基氯化铵后，不仅对自身消毒剂敏感性降低，且多数菌株也对环丙沙星、氯霉素等抗菌药物耐药[3]。耐碳青霉烯肺炎克雷伯菌长期暴露于氯己定后不仅对氯己定产生耐药，还有菌株对粘菌素敏感性降低[46]。

葡萄球菌属的共耐药现象也较为常见。金黄色葡萄球菌长期暴露在低水平氯己定、过氧化氢和三氯生等消毒剂下发现其至少对一种抗生素的耐药性增加[47]。凝固酶阴性葡萄球菌分别暴露于亚抑制浓度氯己定-葡萄糖酸盐(chlorhexidine-digluconate, CHDG)和苯扎氯铵后，不仅对自身使用的消毒剂耐药，还提高了对另外一种消毒剂和部分抗生素耐药性[48]。

同样发现铜绿假单胞菌暴露于亚致死浓度的苯扎氯铵后，对庆大霉素以及环丙沙星等耐药性显著增加[49]。铜绿假单胞菌暴露于亚抑制浓度的次氯酸钠后，对 14 种抗生素中的 9 种抗生素产生耐药性[50]。假单胞菌暴露在亚抑菌浓度的二癸基氯化铵和次氯酸钠后，观察到该菌对粘菌素、头孢他啶、美罗培南、庆大霉素和环丙沙星等抗菌药物的敏感性降低[51]。

将从有机食品中分离出的包括肠杆菌属、肠球菌属、芽胞杆菌属、产酸克雷伯菌等 76 株对消毒剂敏感的细菌反复暴露于浓度不断增加的苯扎氯铵和氯化十六烷基吡啶后发现，经苯扎氯铵处理后的菌株对其 MIC 增加了 4–50 倍，经氯化十六烷基吡啶处理后的菌株对其 MIC 最高增加超过 100 倍，且经苯扎氯铵处理后的菌株还表现出对氨苄西林和头孢噻肟等抗生素敏感性降低[52]。饮用水经过氯化消毒处理后，由于各种因素导致耐氯性细菌的产生，更糟糕的是，由于共选择作用，耐氯性细菌也可能提高对常见抗生素的耐药性，产生公共卫生风险[53]。

4.2 消毒剂和抗生素共耐药机制

细菌对消毒剂的耐药性涉及到膜通透性的改变、外排作用、形成生物被膜等机制。由于细菌对抗生素和消毒剂的耐药机制相似，所以对消毒剂的耐药性很可能也参与到对抗生素的共耐药中。弯曲菌在镇疫醛、复方戊二醛、百毒杀的长期选择压力下，除了对本身消毒剂耐药之外，还表现出对红霉素、环丙沙星等抗菌药物的敏感性降低。检测发现消毒剂诱导后的耐药菌株与诱导前的亲本菌株相比，外膜蛋白、外排泵和生物被膜相关基因存在差异表达，证明外膜蛋白变化、外排泵活性以及生物被膜形成参与到消毒剂诱导空肠弯曲菌对抗菌药物共耐药中[54]。研究发现，细菌对消毒剂和抗生素的共耐药机制涉及到细胞表型、外排泵活性和生物被膜的变化以及基因突变或过表达等方面。表 2 对细菌暴露于消毒剂后对抗生素产生共耐药涉及到的几种机制进行了整理。因为菌株之间的生长特性不同，消毒剂作用机制的差异性，所以导致了不同菌株经不同消毒剂处理后显示出不同的变化，相关耐药机制还需进一步研究。

细胞表型的变化包括细胞膜通透性降低、细胞表面疏水性以及外膜蛋白改变[49]。研究发现大肠埃希菌长期暴露于低浓度三氯生后，不仅对三氯生耐药，而且对红霉素、氯霉素等也产生耐药，检测发现其外膜和内膜通透性降低，而且外排活性也增强[55]。大肠埃希菌暴露于亚抑制浓度不断增加的磷酸三钠(trisodium phosphate, TSP)、亚硝酸钠(sodium nitrite, SNI)和次氯酸钠后，对本身 3 种消毒剂以及一系列抗生素的敏感性均降低。这可能与细胞膜通透性降低以及外排泵的表达增加有关[56]。洗必泰和氯化十六烷基吡啶处理放线菌和链球菌后，二者对四环素、阿莫西林的敏感性下降，检测发现消毒剂处理后细菌细胞表面疏水性增强[57]。

肺炎克雷伯菌在氯已定压力下，通过 *cepA* 基因编码的外排作用进而对粘菌素产生耐药[58]。用亚抑制浓度的苯扎氯铵处理铜绿假单胞菌后，发现其对自身消毒剂以及环丙沙星、多粘菌素、氯霉素等抗菌药物的耐药性增加，对其进行分析发现 *mexCD-oprJ* 多药外排泵基因过表达导致对苯扎氯铵外排作用增强，*pmrB* 基因发生突变导致外膜上的负电荷减少[59]。用亚致死浓度甲醛和戊二醛的季铵盐(a quaternary ammonium disinfectant containing formaldehyde and glutaraldehyde, QACFG)等消毒剂处理沙门菌后发现其 AcrAB 和 TolC 外排系统表达水平升高，外膜蛋白水平降低，对环丙沙星、四环素等抗菌药物敏感性降低[60]。

铜绿假单胞菌经过亚致死浓度的苯扎氯铵处理后显示对部分抗生素敏感性降低，分析发现部分菌株细胞表面疏水性增强，还有一些菌株生物被膜形成能力增强[49]。铜绿假单胞菌在暴露于亚抑制浓度的次氯酸钠后，其对 14 种抗生素中的 9 种抗生素耐药程度升高，检测发现大部分细菌有生物被膜形成[50]。亚抑制浓度三氯生、苯扎氯铵等消毒剂处理后的弯曲菌对卡那霉素和链霉素的敏感性降低，发现耐药菌株不仅形态和外膜蛋白发生变化，生物被膜形成也增强[61]。许多研究已证实生物被膜形成是细菌对消毒剂耐药的机制之一，但对生物被膜在抗菌药物共耐药中的作用上研究较少。

表 2　细菌对消毒剂和抗生素共耐药机制

Table 2　Mechanisms of bacterial co-resistance to disinfectants and antibiotics

Disinfectant	Antibiotic	Co-resistance mechanism	Reference
Benzalkonium chloride	Gentamicin, ciprofloxacin, etc.	Decreased cell membrane permeability, changes in membrane proteins and cell surface hydrophobicity	[49,55-57,60-62]
Triclosan	Erythromycin, chloramphenicol, etc.		
Trisodium phosphate, sodium nitrite, sodium hypochlorite	Gentamicin, ciprofloxacin, etc.		
Chlorhexidine, etc.	Tetracycline, amoxicillin, etc.		
Chlorhexidine	Colistin	Enhance efflux activity	[55-56,58-60]
Benzalkonium chloride	Ciprofloxacin, polymyxin, etc.		
A quaternary ammonium disinfectant containing formaldehyde and glutaraldehyde	Ciprofloxacin, tetracycline, etc.		
Benzalkonium chloride	Ciprofloxacin, gentamicin, etc.	Biofilm formation	[49-50,61]
Triclosan, benzalkonium chloride	Kanamycin, streptomycin		
Sodium hypochlorite	Meropenem, ciprofloxacin, etc.		
Quaternary ammonium compound, etc.	Quinolones	Gene mutation or overexpression	[45,59,62-63]
Dodecyltrimethylammonium chloride	Tetracycline, chloramphenicol		
Triclosan	Amoxicillin, chloramphenicol, etc.		

沙门菌暴露于亚抑制浓度的季铵盐类等消毒剂期间，部分抗生素耐药突变体菌株中 3 个基因(*fabI*、*ramR* 和 *gyrA*)发生突变，其中 *ramR* 基因是调节 AcrAB-TolC 多药耐药外排系统的转录激活因子[45]。经十二烷基三甲基氯化铵(dodecyltrimethylammonium chloride, DTAC)处理后，大肠埃希菌对四环素和氯霉素的耐药性增强，分析发现消毒剂的处理促进了 RP4 耐药质粒的接合转移，产生多药耐药[62]。大肠埃希菌经过三氯生处理后，其对阿莫西林以及氯霉素等耐药性增加，对耐药菌株进行测序发现 *ampC* 和 *acrR* 等基因发生突变，相关基因缺失和过表达导致对抗菌药物共耐药[63]。

综上所述，细菌共耐药可能不仅仅只涉及一种机制，这使得共耐药变得更复杂。共耐药的产生是一个长期的过程，需要我们按照说明正确使用消毒剂和密切关注可能会产生的变化。研究发现在农业环境中正确地使用消毒剂不会促进抗生素耐药性，也不会降低大肠埃希菌对消毒剂的敏感性[64]。

5 结论与展望

一方面，消毒剂在日常生活中的使用极大地提高了生活质量，而另一方面，消毒剂的使用也带来各种负面问题，例如不合理地使用导致消毒剂耐药性的产生；另外消毒剂使用时会分解产生许多危害极大的消毒副产物(disinfection by-products, DBPs)[65]，给日常生活以及医院治疗带来更大的挑战。如果细菌对所使用的消毒剂不再敏感，食源性疾病将成为家常便饭，生命和健康将受到严重的威胁。消毒剂以及消毒副产物通过城市排水系统或地表径流进入河流，使河流受到污染。此外，每年使用的季铵盐类消毒剂中大约 75%排放到废水处理系统中，而其余的直接排放到环境中，且废水和环境中的季铵盐类消毒剂的浓度均明显低于应用浓度[66]，导致耐消毒剂细菌的产生，对环境微生物生态多样性产生巨大的影响，使环境的污染问题发生恶性循环。

防止出现消毒剂耐药细菌以及共耐药细菌已成为一个全球性的战略问题。本综述就细菌对消毒剂的耐药机制、消毒剂耐药性的产生和传播、细菌对消毒剂和抗生素共耐药几个方面进行了相关的论述。细菌对消毒剂的耐药性相比较于抗生素耐药性，有可能更加复杂，还需进一步挖掘。虽然目前对上述内容已有很多的研究进展，但仍存在以下问题：在消毒剂方面，大多数研究报道集中于季铵盐类消毒剂以及其他阳离子消毒剂，对于其他类型的消毒剂报道不是很多；另外，所研究的细菌并没有很强的代表性，很难弄清不同实际条件下细菌对消毒剂的主要耐药机制。尽管已经阐明了一些机制，但是对消毒剂耐药基因水平转移的研究非常有限。耐药基因是否可以通过转化以及转导等方式来进行水平转移，目前还无报道。细菌适应环境压力后可导致对抗菌药物或消毒剂产生耐药[67-68]。但是环境因素对于共耐药的影响尚无相关研究。综上所述，今后我们应该加强针对不同消毒剂和细菌的耐药性研究，扩大研究范围，利用 CRISPR-Cas 系统与其他基因编辑技术深入了解消毒剂耐药性背后的分子机制[37]，阐明消毒剂耐药基因的可转移性以限制这些可移动遗传元件的传播，深入探索细菌对消毒剂和抗生素共耐药的机制，制定合理使用消毒剂的策略，积极寻找有效的消毒产品或者替代产品，为科学有效使用消毒剂和减少消毒剂耐药性风险提供理论支持。

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