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在线全文

生物膜相关院内感染的新型消毒技术研究进展*

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【摘要】 临床上生物膜的消除是控制医院感染至关重要的一环。生物膜一旦在管腔型器械中定植，采用传统消毒方法难以将其去除。传统的消毒方法现面临耐药性、腐蚀性、细胞毒性、消毒副产物残留和环境污染等一系列的问题。因此，开发针对生物膜清除的新型消毒技术具有重要意义。微酸性电解水、等离子体技术、表面改性技术、纳米材料消毒技术、噬菌体消毒技术、酶解消毒技术等新型消毒技术不断涌现，这些技术通过活性氧爆发、光催化氧化、物理破坏及生物靶向等机制协同增效，在对抗生物膜方面表现优异。本研究综述了上述新型消毒技术的特点、机制及潜在应用场景，并重点关注对医院环境表面常见致病菌生物膜的作用效果，为这些消毒技术的实际应用转化以及消毒新策略的开发提供参考的依据。

【关键词】 生物膜 化学消毒技术 物理消毒技术 生物消毒技术 综述

Advances in Novel Disinfection Technologies for Biofilm-Associated Nosocomial Infections

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[Abstract] The elimination of biofilms is a crucial step in controlling hospital-acquired infections. Once biofilms colonize luminal instruments, it is difficult to remove them using traditional disinfection methods. Conventional disinfection approaches now face a series of challenges, including microbial resistance, corrosiveness, cytotoxicity, residual disinfection byproducts, and environmental pollution. Therefore, developing novel disinfection technologies specifically targeting biofilm removal is vitally important. New disinfection technologies, such as slightly acidic electrolyzed water, plasma technology, surface modification techniques, nanomaterial-based disinfection, bacteriophage disinfection, and enzymatic disinfection, are constantly emerging. These technologies exhibit excellent performance against biofilms by leveraging the synergistic effects of multiple mechanisms, including the reactive oxygen species (ROS) burst, photocatalytic oxidation, physical disruption, and biological targeting. This review summarizes the characteristics, underlying mechanisms, and potential application scenarios of these novel disinfection technologies, with a particular focus on their effects against biofilms formed by common pathogenic bacteria on surfaces in hospital settings. It aims to provide a reference basis for the practical application and translation of these disinfection technologies and the development of new disinfection strategies.

[Key words] Biofilm Chemical disinfection technology Physical disinfection technology Biological disinfection technology Review

生物膜由微生物群落及其分泌的胞外聚合物（extracellular polymeric substance, EPS）组成。EPS复杂的空间结构不仅为微生物群落提供了物理屏障，也是生物膜耐受消毒剂的主要原因[1]。研究显示，生物膜内微生物的抵抗力可以提高10 ~ 1 000倍[2]。美国国立卫生研究院指出，生物膜的形成与65%的微生物感染和80%的慢性疾病有关[3]。生物膜广泛存在于重复使用的医疗器械及管道系统中，已经成为院内感染防控的难题[4-5]。

传统的消毒方案包括次氯酸钠（NaClO）、酒精、过氧化氢、紫外线辐射、臭氧等[6-7]。EPS中的多种有机物与NaClO相互作用从而降低NaClO的渗透速率，若作用浓度

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或接触时间不足将导致消毒失败[8]；紫外线对生物膜的穿透能力弱，且含汞的灯管存在环境污染问题[9]，这些消毒方案在应对生物膜感染方面有一定局限性(表1)[10-12]。此外，传统消毒方法的单独使用并不能实现对成熟生物膜100%的清除[13]，因此，开发新型的消毒替代方案从而对生物膜实现有效的控制是目前研究的焦点[14-16]。

表 1　几种常见消毒方法的优缺点

Table 1　The advantages and disadvantages of several common disinfection methods

Index	NaClO	O_3	UV	H_2O_2
Simplicity	√	×	√	√
Low cost	√	×	×	√
Germicidal efficacy	√	√	√	×
Residual effect	√	×	×	×
Disinfection byproducts	×	√	√	√
Environmental friendliness	×	×	×	√
Corrosiveness	×	×*	√	×*
Irritancy	×	×	×	√
Cytotoxicity	×	×	×	×
Biofilm penetration ability	×	√	×	√
Biofilm drug resistance	×	—	×	×

√ indicates an advantage; × indicates a challenge/disadvantage; ×* indicates that the method shows a disadvantage at high concentrations; — indicates that no relevant research is currently available.

为应对传统消毒策略的局限性，一系列基于传统消毒方法改进或新机制、新材料、新剂型的消毒技术不断被开发，参考相关文献[17-20]，我们将相关原理绘制为图1。本文回顾了近年来开发的生物膜有效消除技术，综述了这些技术抗生物膜的机制、优缺点以及适用范围，重点关注其对常见生物膜院感菌的作用效果，探讨了这些技术的应用前景及潜在改进方向，为后续更多新方法的开发提供参考。

1　物理与材料学消毒技术

1.1　等离子体消毒技术

等离子体是物质的第四态，最常用于灭菌的是低温等离子体。研究指出，常压或三分之一脉冲等离子体更适用于医疗环境的消毒[21]。BHATT等[22]研究出了一种新型氩等离子体活化气体，该气体能够在9 min内分散内窥镜通道中金黄色葡萄球菌(*taphylococcus aureus*, SA)、铜绿假单胞菌(*Pseudomonas aeruginosa*, PA)和大肠杆菌(*Escherichia coli*, EC)的生物膜并抑制其再生，同时不对管道形态造成任何改变。由于干燥的生物膜往往具有更强的抵抗力，用液体等离子体能够避免生物膜干燥，从而达到更好的清除效果。NOOPAN等[20]通过低温等离子体灭菌系统显著降低了附着在牙科水线水管表面生物膜的数量和活性。等离子体活化水(plasma-activated water, PAW)能够通过活性氧和活性氮(reactive oxygen and

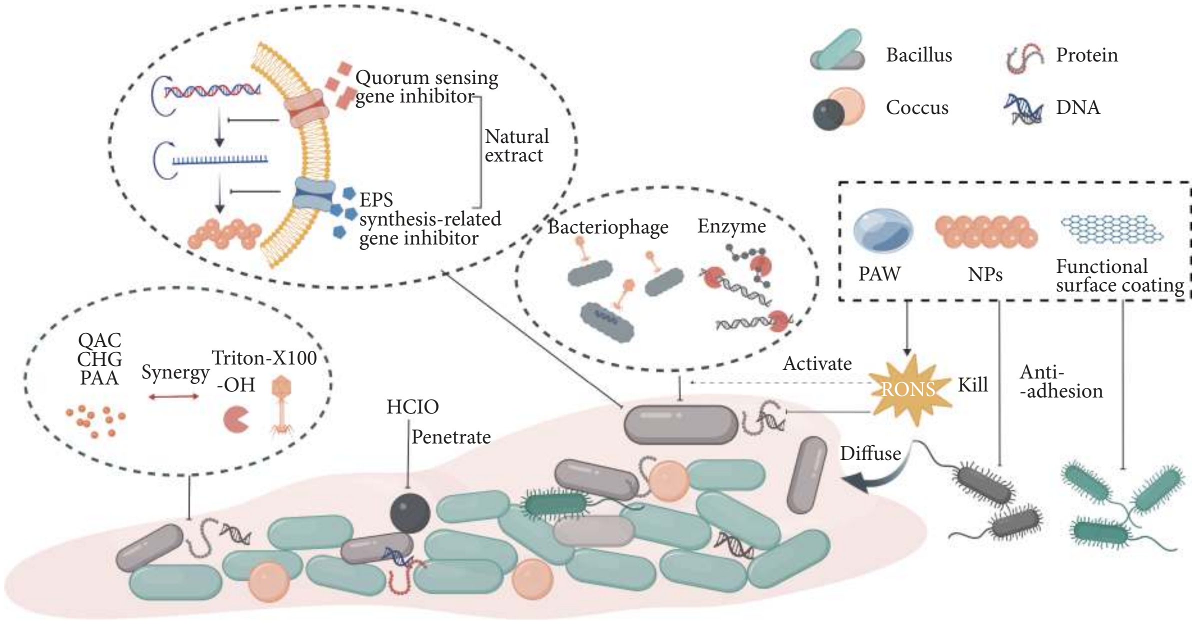

图 1　各类新型消毒技术抗生物膜机制示意图

Fig 1　Schematic diagram of the anti-biofilm mechanisms of various new disinfection technologies

QAC: quaternary ammonium compound; CHG: chlorhexidine gluconate; PAA: peracetic acid; PAW: plasma activated water; NPs: nanoparticles; RONS: reactive oxygen and nitrogen species.

nitrogen species, RONS)直接渗透到生物膜内部杀菌或通过破坏EPS从而使内部细菌恢复浮游状态[23]。NORTHAGE等[24]在此基础上进一步改进,用等离子体对过氧乙酸进行活化得到了效果优于PAW的等离子体活化液体(plasma-activated liquid, PAL),使用PAL对内窥镜进行消毒,3 min内即可达到与市售的pH缓冲过氧乙酸溶液(DIS: Olympus EndoAct/EndoDis, Olympus Surgical Technologies)处理5 min相当的抗生物膜效果。相较于传统消毒方法,PAL还将生物膜的再生率降低了一个数量级。此外,有研究发现等离子体技术还可以通过激活EC中的λ噬菌体发生级联反应,从而增强对该菌的灭活及其生物膜的破坏[25]。

1.2 纳米材料技术

研究表明,抗黏附纳米、聚合物接枝纳米、生物活性纳米、活性氮氧物释放纳米和响应性纳米等纳米材料通过多种机制抑制生物膜[19],对鲍曼不动杆菌(*Acinetobacter baumannii*, AB)、肺炎克雷伯菌(*Klebsiella Pneumoniae*, KP)、EC、PA、SA等多种生物膜均具有抑制作用[26-28]。研究显示,100 μg/mL的银纳米颗粒可使EPS合成减少64% ~ 86%[29]。LEE等[30]发现ZnO纳米颗粒可通过改变细胞疏水性、调控基因表达和抑制初始黏附来抑制PA生物膜,通过抑制SA和EC细菌的生长来抑制其生物膜的形成。

在临床应用中需根据具体场景来选择合适的纳米材料。比如,在颌面消毒领域,已知二氧化钛纳米颗粒可以提高有机硅弹性体的硬度和撕裂强度,CEVIK等[31]将纳米钛掺入硅胶中,不仅提高了颌面材料的性能,还通过二氧化钛与葡萄糖酸氯己定(chlorhexidine gluconate, CHG)的协同达到更好的抗生物膜效果;而在血液透析管道消毒方面,ZnO纳米颗粒则被用作功能性载体,通过结合天然一氧化氮(NO)供体控制NO的释放,增强对隧道式透析导管枢纽区域PA和SA生物膜的清除效率[32]。

1.3 表面改性技术

大量研究证明,预防生物膜的形成比生物膜形成后再利用消毒剂杀灭更为有效[2]。因此,通过表面改性防止生物膜的定植成为研究热点。目前表面改性技术主要围绕两个方向展开:一是通过降低表面自由能抑制细菌初始黏附,二是通过引入活性官能团实现长效杀菌。在低表面自由能的改性方面,YABUNE等[33]研发了一款应用于牙科水线的聚偏氟乙烯涂层管道,其低表面自由能可以减少有机物和细菌的非特异性附着,实验表明该涂层对生物膜的抑制率达85%以上。有机硒被证明可以抑制细菌对不同聚合物材料的附着,TRAN等[34]将有机硒掺入到聚丙烯隐形眼镜盒中,发现其能够抑制嗜麦芽窄食单胞菌(*Stenotrophomonas maltophilia*, SM)、PA、SA等多种细菌的生物膜。在活性官能团改性方面,LUO等[35]设计了一款N-卤胺基氯化再生循环抗菌聚氨酯(PU)管道,在PU管道内表面引入甲基丙烯酰胺聚合物,经氯化形成N-卤胺结构。实验发现该技术对PA生物膜的抑制时效达4周以上,并可通过重复氯化恢复抗菌功能。

2 生物与酶解技术

2.1 噬菌体

噬菌体能够靶向杀灭目标宿主菌。研究发现,噬菌体对凝固酶阴性葡萄球菌(coagulase negative staphylococci, CNS)、耐甲氧西林金黄色葡萄球菌(methicillin-resistant *Staphylococcus aureus*, MRSA)、白色念珠菌(*Candida albicans*, CA)、KP、AB、PA、EC[36-38]形成的生物膜均具有抑制作用。为了使噬菌体在特定条件下释放,ZUO等[39]将噬菌体封装在壳聚糖中开发了pH响应型噬菌体,使噬菌体在pH5时释放,减少了PA生物膜的生物量及覆盖率。噬菌体基因组的模块化设计可进一步优化噬菌体的性能。SUN等[40]对M13噬菌体尾纤维蛋白进行定向修饰得到多价噬菌体,实现了工程化噬菌体向PA主导的双菌种生物膜内部细菌的靶向递送,其在高浓度下通过下调群体感应(quorum sensing, QS)和EPS分泌相关基因抑制生物膜的再生。然而,浓度是在使用噬菌体制剂时需要重点考虑的一个问题。ZHANG等[41]的研究发现,低浓度的噬菌体可能会刺激QS基因和EPS分泌相关基因表达上调导致PA和EC生物膜出现反向生长和致密化,从而加剧其对含氯消毒剂的抵抗力。除了直接使用噬菌体,噬菌体的基因产物也可用于杀菌。比如,噬菌体内溶素被发现能够在体外靶向细菌,水解宿主细胞壁从而导致细菌死亡[42]。

2.2 天然提取物

天然提取物的抗菌机制多样,一些天然提取物具有潜在的抗生物膜功效。研究发现,弯子木提取物中的没食子酸可通过调节胞间黏附素操纵子的表达来抑制MRSA生物膜的形成,从而便于其他抗菌化合物对生物膜的渗透[43];黄芩提取物中的黄芩苷、人参提取物中的人参皂苷CK可通过干扰分枝菌酸的生物合成抑制脓肿分枝杆菌的生长及其生物膜的形成[44-45];百里香提取物中的百里香酚通过淬灭QS抑制多种临床耐药菌株的生物膜[46]。

传统的消毒方法可干扰有机硅的颜色稳定性、硬度、弹性和粘性等,天然提取物在这一方面表现出色,尤其适用于颌面硅胶材料的消毒。例如,使用10%巴西绿

蜂胶酒精溶液浸泡5 min可完全清除硅胶表面的SA生物膜，且对材料性能无显著影响[47]。百里香衍生草药消毒剂有效作用于SA和CA生物膜，且几乎不会造成有机硅的颜色变化[48]。不同浓度的提取物在抗菌性能和美学耐久性的表现上差异显著，未来应精确界定其最佳浓度范围以平衡其抗菌性和材料的相容性。

2.3 酶解技术

使用组合酶制剂对EPS进行降解有助于提高消毒效率。STIEFEL等[49]在96孔板和内窥镜通道中评估酶对SA和PA生物膜的清除效果，发现使用单一酶仅能去除SA生物膜，使用组合酶方能去除PA生物膜。不同材质表面生物膜的去除效率不同。IÑIGUEZ-MORENO等[50]发现蛋白酶和α-淀粉酶混合物对不锈钢表面多菌种生物膜的去除率为93.4%～96.3%，而对于聚丙烯B表面的生物膜去除率仅为12.2%。此外，酶的效果易受环境影响，因此，在开发试剂时要考虑其在实际消毒场景的作用效果。MECHMECHANI等[51]将酶进行微胶囊化包埋实现其对特定环境的响应，DEL POZO等[52]将酶负载在水凝胶上以实现酶的按需释放。这些方法均有效增强了酶的稳定性和活性。

此外，还可以通过构建新型的工程酶用于生物膜的清除。比如，Al-MADBOLY等[53]使用模块化组装技术开发了一类新的嵌合裂解酶，增强了裂解酶抗MRSA生物膜的活性和特异性。FANG等[54]则尝试合成了内酯酶和酰化酶等群体感应猝灭酶，降解信号分子（如酰基同丝氨酸内酯）破坏细菌间的通讯，从而阻止生物膜的形成。然而，LIM等[55]观察到在酶存在的情况下生物膜形成增加，提示了新酶制剂在投入使用前需要进行系统的评估。

3 化学消毒新技术

3.1 微酸性电解水（slightly acidic electrolyzed water, SAEW）

目前以NaClO为代表的含氯消毒剂面临着环境污染、安全性等问题，相对而言，次氯酸（HClO）消毒后无化学残留，对人体和环境更安全。电中性的HClO能够破坏生物膜并穿透细胞壁，而带负电的$\mathrm{ClO^-}$则无法穿透细胞壁，因此，HClO的杀菌能力是$\mathrm{ClO^-}$的80～100倍[56]。HClO对MRSA的最小杀菌浓度（minimum bactericidal concentration, MBC）范围为0.1～2.8 μg/mL，远远低于NaClO的500 μg/mL[57]。NaClO在化学残留、腐蚀性等方面的局限性催生了以HClO为主导的新型消毒体系的发展。HClO在SAEW中占比达90%以上，是SAEW的主要杀菌成分。OKANDA等[58]研究将SAEW应用于内窥镜的消毒，并且证明了SAEW能降解EPS中的藻酸盐，对内窥镜中的PA生物膜实现有效清除。为充分发挥SAEW的安全性优势，可将SAEW应用于口腔接触器械生物膜的消除[58]。

3.2 复合消毒剂

随着生物膜的耐药问题日益严重，使用单一的化学消毒剂很难达到对生物膜的完全清除，多种消毒策略联用可能是减少生物膜耐药性的有效策略。化学组合制剂协同、化学-物理协同、化学-生物协同等联合消毒策略可能更有利于生物膜的清除。一方面，高浓度的单一消毒剂容易引发细菌产生耐药性并增加生物膜的形成，多种消毒策略联用可以降低各组分使用浓度；另一方面，使用组合策略能够通过多机制协同作用应对生物膜复杂的环境。

3.2.1 化学组合制剂协同消毒技术

化学组合制剂是最常见的联合策略，可通过多组分作用靶点互补发挥更好的灭菌作用。比如，已知活性溴化物形成的有害消毒副产物低于活性氯化物，但是活性溴化物消除生物膜的能力有限。基于此，SHUKLA等[59]发现非离子聚环氧乙烷表面活性剂Triton-X100能够提高生物膜基质扩散性及消毒剂渗透效率，显著增强活性溴化物对PA生物膜的清除能力。季铵盐消毒剂是一种中低效消毒剂，为提高季铵盐消毒剂的消毒效果，CHAGGAR等[60]研究了其与醇类的协同作用，发现乙醇可通过溶解生物膜中的脂质来破坏生物膜完整性，从而增加季铵盐消毒剂对SA和PA生物膜的杀灭效率，这种组合也对结核和真菌有杀灭作用。基于作用机制互补的组合消毒策略已成为研究热点，未来需着力探明各消毒剂之间的协同作用机制，并进一步研究其在各个消毒场景下的适用性。

3.2.2 化学-物理协同消毒技术

化学-物理协同消毒技术以物理手段激活或增强化学试剂的反应活性为核心，通过整合化学消毒剂与物理能量以达到增强消毒效果、减少化学残留的目的。现已将等离子体激活消毒、光催化氧化和纳米载药缓释系统等技术应用在生物膜的消除中。

NORTHAGE等[24]采用等离子体-过氧乙酸复合技术消除内窥镜内的生物膜，该技术可降低过氧乙酸的使用浓度，减少高浓度过氧乙酸对内窥镜的损坏。IBÁÑEZ-CERVANTES等[61]探索了氯己定和光动力法联合抗钛盘表面生物膜的效果，发现氯己定与细菌细胞壁的结合可增加细菌对光敏剂的通透性，从而有效降低钛盘表面的生物膜活力；臭氧作为气态/液态双效消毒剂，对PA、SA、 AB及KP的生物膜均有抑制作用,然而,臭氧在水中的溶解性和稳定性限制了其消毒效果。微纳米气泡具有稳定性高、气液传质效率高以及可产生活性自由基等优点。ALKAN等[62]尝试通过将臭氧和微纳米气泡技术结合以增强臭氧的稳定性。相较于传统大气泡的臭氧,微纳米气泡的臭氧可在低浓度下实现较高的消毒效率,应用时,臭氧剂量和反应器尺寸都将减小。除了抑制常见的细菌生物膜,这种气泡还能够抑制CA早期生物膜的形成[63]。值得注意的是,由于微纳米气泡增加了反应的接触面积,该技术可能会导致更多消毒副产物(如溴酸盐)的产生,研究发现氨的加入可以一定程度上抑制气泡臭氧化过程中溴酸盐的生成[64],因此,在臭氧微气泡化过程中添加氨来减少消毒副产物有助于微纳米臭氧气泡技术的广泛推广。

3.2.3　化学-生物协同消毒技术

通过生物技术靶向破坏生物活性成分(如噬菌体、天然提取物、酶等)可增强化学消毒剂的渗透与杀菌效率。STACHLER等[65]发现在使用化学消毒剂前施用噬菌体可使湿生物膜中的细菌数量减少,并防止干生物膜的再生。IÑIGUEZ-MORENO等[50]通过在过氧乙酸中增加蛋白酶和淀粉酶实现对多菌种生物膜的有效去除;从骆驼蓬种子中提取的β-咔啉类生物碱单独使用时消毒效果有限,联用CHG后对SA浮游菌和生物膜的MIC分别降低至原来的1/4 ~ 1/8和1/4 ~ 1/16,并杀死了生物膜内绝大多数的细菌[66];类似地,DRAGO等[67]研发的赤藓糖醇-氯己定抛光粉末对PA、SA和CA的成熟生物膜清除率分别达70%、77%和45%,这是利用赤藓糖醇减少多糖介导的黏附、破坏微生物的代谢,从而增强抗菌剂的渗透。值得注意的是,通过增加机械喷射能够增强赤藓糖醇-氯己定抛光粉末对生物膜的剥离效率,CA生物膜的清除率增加到65%[68]。

4　结论

生物膜的清除是消毒领域面临的核心挑战之一。当前,新兴技术在消毒效率、渗透效率、环境友好性、腐蚀性、安全性等方面实现较多创新突破,然而不同新技术各自的优势不同,本文列举的相关技术总结见表2,后续研究需针对新技术的不足进行进一步优化。

表 2　新型消毒技术的优势与不足

Table 2　The advantages and disadvantages of new disinfection technologies

Technology	Advantages	Disadvantages
Plasma technology	High sterilization efficiency No toxic residue	Unstable active substances High production cost and energy consumption
Nanomaterials	High sterilization efficiency	Toxicity requires further assessment High cost
Surface modification technology	Long-term prevention of biofilm colonization Reproducible and renewable	Complex modification process May negatively affect material mechanical properties
Phages	Target specificity Being environmentally friendly Low risk of resistance	Host specificity limits broad-spectrum application Sensitivity to environmental conditions Low concentration may lead to resistance risk
Natural extracts	High biocompatibility Environmentally friendly and low toxicity	Significant concentration dependence Complex extraction process and low cost-effectiveness
Enzymatic hydrolysis technology	Environmental protection No residue High efficiency	Sensitivity to the environment High cost of large-scale production Limited effect of a single enzyme, and hence combination use is required
SAEW	High sterilization efficiency No residual chlorine, low cytotoxicity, and no corrosiveness	Low stability High dependence on equipment
Compound disinfectants	Synergistic enhancement Reducing drug resistance Enhancing the penetration of disinfectants	—

SAEW: slightly acidic electrolyzed water. — indicates that no relevant research is available.

目前的研究多局限于单一生物膜的消毒效果,然而,在实际消毒场景中的生物膜往往由多种微生物共同组成,其代谢互作的复杂性可能增强对消毒剂的抗性[69]。生物膜的生长阶段显著影响消毒效能[70],成熟的生物膜可能需要更加复杂的消毒手段,现有研究缺乏对生物膜整个形成周期消毒效果的研究。未来研究将以提高消毒效率、降低毒副作用、减少能耗成本为着力点,深入探究多种消毒技术的协同作用,以应对复杂的环境。同时建立更贴近真实场景的多菌种生物膜模型,并评估消毒策略对不同生长阶段生物膜的清除效果。通过技术创新和多技术联用并结合多方面性能验证,推进医院感染常见病原菌生物膜消毒策略的逐步完善。

* * *

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