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· 专家论坛 ·

# 抗菌-再矿化-渗透协同策略治疗牙体硬组织疾病的研究进展

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**【摘要】** 本文系统阐述了抗菌-再矿化-渗透协同策略在牙体硬组织疾病防治中的研究进展。龋病是由致龋菌引起的慢性感染性疾病, 传统氟化物防治手段因抗菌能力有限、深层渗透性差, 难以有效阻断深层龋病进展。为此, 研究者提出整合抗菌、再矿化与渗透三大功能的龋病阻断策略, 通过金属离子、抗菌肽、纳米材料等抗菌成分抑制致龋菌生物活性; 利用生物活性玻璃、无定形磷酸钙等材料诱导羟基磷灰石原位沉积, 促进牙体硬组织再矿化; 并凭借材料的高渗透性深入病变微孔, 形成物理屏障, 从而阻断酸蚀与菌斑再侵袭。该策略不仅适用于早期龋病的微创干预, 也拓展至牙本质敏感、楔状缺损及酸蚀症等非龋性牙体硬组织疾病的治疗。多项体外与动物实验表明, 符合该系统策略理念下的多功能涂层、纳米复合体系等材料能显著提升牙体硬组织疾病的治疗效果。随着仿生材料与智能递送系统的发展, 该策略有望在未来实现更高效的组织结构修复与功能重建, 推动牙体硬组织疾病治疗向精准化、微创化和智能化方向迈进。

**【关键词】** 抗菌; 再矿化; 渗透性; 金属离子; 抗菌肽; 纳米材料; 生物活性玻璃; 无定形磷酸钙; 龋病; 龋病阻断; 牙本质敏感; 楔状缺损; 酸蚀症

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**Research advances on a antibacterial-remineralization-infiltration synergistic strategy to treat dental hard tissue diseases** ZHANG Xu, YANG Qingyi. Tianjin Key Laboratory of Oral Soft and Hard Tissues Restoration and Regeneration, Tianjin Medical University School and Hospital of Stomatology, Tianjin 300070, China

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**【Abstract】** This paper reviews research progress on a antibacterial-remineralization-infiltration synergistic strategy for the prevention and treatment of dental hard tissue diseases. Dental caries is a chronic infectious disease caused by cariogenic bacteria. Traditional fluoride prevention methods are unable to effectively halt the progression of deep caries due to limited antibacterial capacity and poor deep penetration. To address this, researchers have proposed an interruption of dental caries strategy that integrates antibacterial, remineralization, and infiltration functions. This approach utilizes antibacterial components, such as metal ions, antibacterial peptides, and nanoparticles, to suppress cariogenic bacterial activity. Bioactive glass and amorphous calcium phosphate materials induce in situ hydroxyapatite deposition to achieve dental hard tissue remineralization. Simultaneously, the materials penetrate deep into the micro-pores of a lesion via high permeability, forming a physical barrier that blocks acid erosion and plaque re-invasion. This strategy is applicable not only for minimally invasive intervention in early caries but also extends to treating non-carious conditions, such as dentine hypersensitivity, wedge-shaped defect, and tooth erosion. Multiple *in vitro* and animal studies demonstrate that multifunctional coatings and nanocomposite systems developed under this systemic approach significantly enhance treatment efficacy for dental hard tissue diseases. Future advancements in biomimetic materials and

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smart delivery systems hold promise for achieving higher levels of structure-function reconstruction, which will propel dental hard tissue disease treatment toward precision, minimally invasive, and intelligent approaches.

**【Key words】** antibacterial; remineralization; infiltration; metal ions; antibacterial peptides; nanomaterials; bioactive glass; amorphous calcium phosphate; dental caries; interrupt dental caries; dentine hypersensitivity; wedge-shaped defect; dental erosion

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牙体硬组织疾病,尤其是龋病,至今仍是全球最常见的口腔健康问题之一,与多种全身系统性疾病关系密切<sup>[1]</sup>。龋病的发生发展在本质上源于口腔微生物群失衡,致龋菌代谢产酸增加,导致牙釉质与牙本质脱矿,最终形成不可逆的组织缺损<sup>[2]</sup>。目前,氟化物等传统防治手段主要通过促进再矿化和抑制脱矿来发挥作用,但其抗菌能力有限,且对已形成的深层病变渗透性差<sup>[3]</sup>。因此,探索兼具抗菌与再矿化功能的高渗透性综合性策略成为近年来研究的重点。基于以上背景,Lu等<sup>[4]</sup>提出了龋病阻断(interrupt dental caries, IDC)的概念,强调通过运用具有抗菌、再矿化、以及良好渗透性的材料和技术,阻断疾病进展并恢复口腔微环境的动态平衡。因此,符合龋病阻断理念的干预材料应具备以下性能:①稳定且持续的抗菌能力;②高效输送大量钙、磷离子以实现病变区域再

矿化;③优异的渗透性,以有效封闭脱矿的牙釉质孔隙和牙本质小管。值得注意的是,抗菌-再矿化-渗透协同策略的适用范围并不仅限于龋病。近年研究显示,该策略在多种非龋性牙体硬组织病变中亦具有潜在价值(图1)。例如,在牙本质过敏的防治中,渗透性材料与再矿化剂的联合应用能够有效封闭牙本质小管并增强组织抗酸性<sup>[5-6]</sup>;在牙齿酸蚀症和楔状缺损的修复中,该策略同样有助于再矿化硬组织并降低继发性损伤风险<sup>[7]</sup>。因此,该协同策略可被视为一种具有普适性的多功能治疗理念,为多类型牙体硬组织疾病的综合防治提供新的可能性。本文旨在阐述近年来关于抗菌-再矿化-渗透协同策略在牙体硬组织疾病防治中的研究进展,重点关注材料学创新、作用机制阐释及临床应用,并对其未来发展方向进行展望,以期对相关研究与临床应用提供参考。

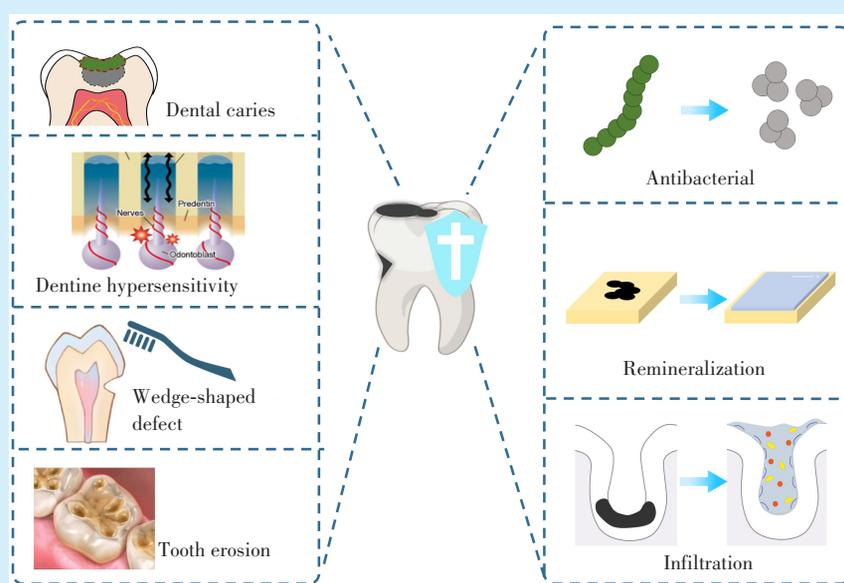


Figure 1 Schematic of an antibacterial-remineralization-infiltration synergistic strategy for treatment of dental hard tissue diseases

图1 抗菌-再矿化-渗透协同策略治疗牙体硬组织疾病的示意图

## 1 抗菌策略

龋病是一种细菌感染性疾病,其发生始于口腔微生态失衡,以致龋菌成为优势菌群并形成生物膜。因此,从病因学层面应用抗菌技术干预龋病进程具有必要性,其有效性直接决定再矿化与渗透干预是否能够在稳定微环境中发挥作用。首先,有效的抗菌作用能够直接抑制变形链球菌、乳酸杆菌等优势致龋菌的定植与代谢活性,从源头上减少致龋性酸性产物的生成。其次,在治疗层面,抗菌材料能够为后续的再矿化过程创造稳定的生物学环境,避免新形成的羟基磷灰石晶体在持续存在的菌斑酸性环境中遭受破坏。

基于此,开发具有持久抗菌活性、可作用于深层生物膜并兼具良好生物安全性的抗菌策略,是实现龋病有效控制的首要前提。含银化合物在口腔医学中的应用已逾一个世纪,广泛用于窝洞消毒、龋病预防与牙本质脱敏等领域<sup>[8-9]</sup>。氟化物除了促进氟磷灰石形成、增强釉质矿化外,还可通过抑制烯醇酶活性干扰糖酵解过程,从而抑制变形链球菌产酸。氟化物与含银化合物的局部应用均被证实能有效预防并延缓龋病进展<sup>[10-11]</sup>。相较于传统含银化合物,银纳米粒子凭借其更大比表面积,作为高效抗菌成分被引入充填树脂与粘接剂中,显著降低继发龋风险<sup>[12]</sup>。其他金属氧化物如氧化锌、氧化铜亦展现出良好的抗菌性能,有助于减少继发龋发生<sup>[13]</sup>。

氯己定作为广谱抗菌剂,通过静电吸附破坏细菌细胞膜通透性,从而发挥广谱抗菌作用,在牙龈炎与牙菌斑控制方面已有广泛应用<sup>[14]</sup>。然而,传统剂型因滞留时间短、组织渗透性差及潜在毒性,临床效果有限。近年来,通过将其载入介孔二氧化硅纳米粒、纳米乳液或pH敏感聚合物等纳米载体,显著提升了其抗生物膜效能与生物安全性<sup>[15-19]</sup>。季铵化合物则依靠其阳离子表面与带负电的细菌膜结合,改变膜通透性,引起细胞破裂<sup>[20]</sup>。例如,由5%甲基丙烯酸二甲氨基六十六烷酯与20%纳米级无定形磷酸钙构成的纳米复合材料,兼具长期抗菌与抑制修复体周围脱矿的作用,适用于继发龋的预防<sup>[13]</sup>。

此外,多种新兴抗菌体系在龋病管理中也显示出重要潜力。例如,具有靶向功能的抗菌肽GL13K被证实可通过静电作用特异性破坏致龋菌细胞膜<sup>[21]</sup>;光动力抗菌疗法利用亚甲基蓝、黑磷纳米片等光敏剂在红光激发下产生活性氧,可有效

渗透并瓦解复杂生物膜结构,还对根管系统等隐蔽区域的感染控制具有独特优势<sup>[22-24]</sup>;氧化铁纳米颗粒、金属纳米酶等具有过氧化物酶活性<sup>[25]</sup>,可在H<sub>2</sub>O<sub>2</sub>存在下催化生成高活性羟基自由基,实现对变形链球菌生物膜的高效清除<sup>[26-28]</sup>。群体感应抑制剂可通过竞争性结合信号受体有效抑制变形链球菌的毒力基因表达与生物膜形成,且不易诱导细菌耐药性<sup>[29]</sup>。这些新型策略不仅拓展了龋病防治的技术路径,也进一步推动了口腔抗菌治疗向精准、长效与微创方向发展。

尽管抗菌材料种类丰富,但当前仍面临若干挑战:①广谱抗菌剂可能干扰口腔共生生态,导致菌群失衡;②耐药性风险尚缺乏长期随访数据;③多数金属纳米材料的长期滞留性尚不明确,生物安全性评估不足等。因此,未来抗菌策略需从单纯杀灭微生物转向调控微生态稳态,并与深层渗透手段协同优化。

## 2 再矿化策略

釉质脱矿是龋病早期阶段最关键且唯一可逆的病理事件<sup>[2]</sup>。随着酸性微环境持续存在,釉质晶体中的钙磷离子不断流失,若不及时恢复矿物平衡,病变将从可逆的表层脱矿逐渐进展为不可逆的结构破坏。因此,再矿化是阻断龋病进程的核心策略<sup>[30]</sup>,其目的不仅在于恢复硬组织的矿化程度与机械强度,还在于提高组织抵抗酸蚀的能力,并减少对传统修复性操作的依赖。尤其在微创和预防理念强调的背景下,如何实现病变深部的有效矿物补充,以及如何在酸性或波动的口腔环境中保持再矿化的稳定性,已成为再矿化材料研发的关键科学问题。

氟化物作为传统再矿化基石,其机制在于酸性环境下氟离子与羟基磷灰石发生同晶置换,形成致密且酸稳定性高的氟磷灰石屏障,从而抑制酸蚀并促进表层再矿化<sup>[31]</sup>。然而,该屏障结构也阻碍了钙磷离子向病变深部渗透,限制了深层修复效果<sup>[32]</sup>;高浓度氟的潜在毒性及对釉质脆性的影响亦引起关注<sup>[33]</sup>。这一局限性促使非氟再矿化策略成为研究新方向。

生物活性玻璃(bioactive glass, BAG)通过释放钙、钠和磷酸盐离子来提高局部pH值,诱导羟基磷灰石沉积<sup>[34]</sup>。粒径小于20 μm的BAG因比表面积更大,离子释放更高效,再矿化效果更优。研究表明,含BAG的牙膏对根面龋的再矿化效果优于

普通含氟牙膏,其矿物离子释放能力更强<sup>[35]</sup>。此外,将BAG掺入粘接剂后能在不影响流变性能的前提下促进牙本质再矿化<sup>[36]</sup>。

仿生再矿化通过模拟釉质天然形成过程,借助蛋白质或其类似物引导无定形矿物前体有序沉积,形成结构与性能接近天然釉质的羟基磷灰石<sup>[37-38]</sup>。无定形磷酸钙(amorphous calcium phosphate, ACP)作为关键矿物前体,可提供钙磷离子,但其在溶液中易转化为磷酸八钙等结晶相<sup>[39]</sup>。酪蛋白磷酸肽-无定形磷酸钙(casein phosphopeptide-amorphous calcium phosphate, CPP-ACP)通过磷酸丝氨酸残基稳定ACP纳米团簇,使其能够渗透至病变深层,并通过非晶相-晶相转变实现仿生矿化<sup>[40]</sup>。该材料可在7 d内显著提升酸蚀釉质的硬度与杨氏模量,但力学性能仍不及天然釉质<sup>[41-42]</sup>。随后,酪蛋白磷酸肽-无定形磷酸氟钙(casein phosphopeptide-amorphous calcium fluoride phosphate, CPP-ACFP)复合体系通过氟与ACP的协同,在保障安全性的同时进一步提升再矿化效率<sup>[43]</sup>。但CPP-ACP诱导沉积的羟基磷灰石晶体取向杂乱,缺乏天然釉质特有的棱柱状阵列与釉柱间有机基质,无法再现生理再矿化过程。

除经典的CPP-ACP外,多种新型ACP体系被开发应用。仿生自组装多肽P11-4可与ACP协同作用,其组装纤维网络为ACP纳米簇提供成核模板,显著提升对早期龋损的渗透修复效果<sup>[44-45]</sup>。聚酰胺胺树枝状聚合物(polyamidoamine dendrimers, PAMAM)稳定的ACP复合材料,通过末端基团与钙离子配位,显著延缓ACP相转化,实现牙本质的再矿化<sup>[46-47]</sup>。表没食子儿茶素没食子酸酯(epigallocatechin gallate, EGCG)具有抗菌特性,其通过稳定钙磷离子可形成EGCG-ACP复合材料,可通过抗菌与再矿化两方面入手管理龋病<sup>[48-49]</sup>。这些ACP基材料通过不同稳定机制与功能改性,显著提升了传统ACP体系的稳定性与修复效能,为龋病微创治疗提供了新的技术路径。

但目前再矿化策略的发展仍存在若干瓶颈:①多数材料难以实现深层病变区域的均匀矿物沉积;②仿生矿化体系在晶体取向、棱柱结构重建方面仍难以完全复制天然釉质;③部分生物活性材料存在成分不稳定、释放不可控等问题。因此,有必要进一步发展精确调控晶体生长方向、稳定矿物前驱体的先进系统,同时对于生理分子调控及仿生组装策略还须进一步探索,以期实现更高层次

度的结构与功能再现。

### 3 渗透策略

当抗菌与再矿化分别作用于病原清除与组织修复时,渗透技术则决定这些活性成分能否真正抵达病灶深部,从而构建整体性的防治体系。早期龋损的病理特征为表层相对完整而体部脱矿,使酸与细菌能够在亚表层持续活动并推动病变进展,仅依赖表面再矿化或单纯抗菌难以有效逆转深层病变。此时治疗的核心在于能否实现对病变体部的有效封闭,或实现能够深入病变区域的干预,以阻断深层酸扩散并限制进一步脱矿。在这一背景下,具有高渗透能力的材料成为必要选择。渗透树脂是一种基于微创理念的牙科治疗技术<sup>[50]</sup>,其核心在于通过低黏度、高渗透性的树脂材料渗入脱矿的釉质微孔中,形成物理屏障,阻断酸和细菌的进一步侵蚀,从而有效阻止龋损进展,甚至促进再矿化。研究表明,渗透树脂联合5%氟化钠清漆在治疗邻面釉质龋损中表现出显著优势,其阻止或逆转病变的能力显著优于单一氟化物治疗,尤其适用于儿童和青少年的乳牙与恒牙,能够在最大限度保留健康牙体组织的前提下控制龋病进展<sup>[51-52]</sup>。将渗透技术置于龋病阻断这一更全面的理论框架中,强调其与抗菌和再矿化策略的协同作用,共同构成龋病管理的三大支柱<sup>[53]</sup>。

近年来,渗透性已成为评估龋病干预材料功能性的先决参数。渗透性不仅是材料的一种物理特性,更是其生物功能能否在病变深处有效发挥的决定性因素。对于再矿化体系,钙-磷离子或前驱矿物颗粒必须突破表层屏障,进入脱矿区体部,才能实现有效的晶体重建;否则仅能形成易剥脱的表面矿物层<sup>[54]</sup>。对于抗菌体系,致龋生物膜的胞外多糖基质天然阻碍药物扩散,纳米级抗菌粒子、抗菌肽递送策略,均需依赖增强的渗透能力以根除深层菌落<sup>[55]</sup>。因此,材料粒径、载体黏度及界面张力等渗透相关指标直接决定其修复力与杀菌力能否在病灶区充分实现<sup>[56]</sup>。理想材料需兼具低黏度与高流动性,以通过毛细作用渗入微隙,同时具备低表面张力,以润湿亲水性组织表面<sup>[57]</sup>。此外,所负载的活性成分必须具备足够小的粒径与良好的单分散性,以确保其能深入脱矿的釉质孔隙或牙本质小管;而通过对材料进行功能化修饰可以增强其与牙体组织的亲和性<sup>[58]</sup>,延长其在病变部位的滞留时间,实现长效作用。

高渗透性树脂能够通过毛细作用快速填充早期龋损的孔隙,阻止酸性物质扩散和矿物溶解,从而防止龋损进一步发展;在牙本质过敏治疗中,渗透性强的脱敏剂能有效封闭牙本质小管,隔离外界刺激<sup>[59]</sup>;在根管治疗中,良好的渗透性确保消毒剂能够深入牙本质小管,清除隐匿的细菌<sup>[60-61]</sup>。只有具备良好渗透性的材料,才能将活性成分有效输送到病变深处。因此,渗透性不仅关乎材料的机械封闭效果,更是其能否在复杂口腔环境中实现长效生物活性的决定因素<sup>[62]</sup>。缺乏足够渗透性的材料难以在早期龋管理、窝沟封闭、粘接修复和根面保护等场景中发挥持久作用,也无法满足当前牙科材料向功能化和仿生设计发展的需求。在龋病阻断理念的推动下,未来材料的研发将更注重渗透性与抗菌、再矿化功能的整合,以实现真正意义上的微创、长效和智能化的龋病管理。

#### 4 抗菌-再矿化-渗透策略的协同机制与功能优势

在龋病管理中,抗菌、再矿化与渗透技术的协同整合已成为提升治疗效果的关键。这三者并非简单叠加,而是在微观结构、口腔微生态及材料学层面形成系统性反馈与协同机制,共同推动修复过程向深层、持久和微创方向发展。

高渗透性材料是实现协同作用的基石。其凭借低黏度特性,通过毛细作用突破釉质和牙本质的结构屏障,将功能组分递送至病变深层。部分材料还具备pH或酶响应特性,能够在致病菌代谢活跃时智能释放抗菌成分<sup>[63-64]</sup>,显著提升对深层生物膜的清除效率;同时保障再矿化前体深入病变体部,避免仅形成易剥脱的表层沉积,从而恢复病变深处组织的晶体完整性。抗菌作用的核心在于生态调控<sup>[65]</sup>。通过抑制致龋菌活性,不仅减少了酸性代谢产物的持续产生,使局部微环境维持于适宜矿物沉积的pH范围,还为再矿化创造了必要条件<sup>[66]</sup>。同时,生物膜厚度的降低也减小了材料渗透的物理阻力<sup>[67]</sup>,间接增强了功能成分的深层递送效率。

再矿化不仅是结构修复的终点,也反向强化抗菌与渗透效果。新形成的矿物相能够致密化脱矿组织,物理性压缩细菌的生存空间并阻碍其定植。更重要的是,仿生矿化形成的稳定界面,为材料的长期滞留提供了理想基底,显著延长了抗菌剂的局部作用时间,从而形成结构性防护屏障。

综上所述,渗透、抗菌与再矿化三者构成了一个逐级推进的协同序列:渗透确保深层递送,抗菌重塑适宜微环境,再矿化实现结构恢复并巩固长期效果。随着智能响应与仿生材料的不断发展,这一协同机制正推动龋病管理从传统表层修复,向深层、持久且生态友好的精准干预模式转变,为口腔硬组织微创修复奠定了新的理论与实践基础。

#### 5 抗菌-再矿化-渗透协同策略在不同牙体硬组织疾病中的应用

##### 5.1 早期龋病的阻断与管理

近年来,龋病管理策略正经历从传统修复性治疗向微创再矿化的根本性转变。在此背景下,一系列受天然生物过程启发、具有多重功能的新型仿生材料被设计与开发。这些材料不仅致力于抑制致病菌,更着眼于主动促进牙体硬组织的结构与功能再生,代表着龋病防治的未来发展方向(表1)。

##### 5.1.1 多肽体系

在早期龋病管理中,治疗策略正从单一干预转向微生物稳态调控、结构稳定与深部再矿化的综合干预。多肽凭借其可设计的分子结构与可整合的功能域,成为实现抗菌-再矿化-渗透协同干预的理想平台<sup>[68]</sup>。早期研究侧重于功能融合,如将没食子酸(gallic acid, GA)与抗菌肽KR12耦联获得GA-KR12,可在抑制致龋菌的同时诱导羟基磷灰石沉积,实现抗菌与再矿化双效协同<sup>[69]</sup>。随后,策略转向深部定位与修复,如经釉原蛋白修饰的聚酰胺胺树枝状聚合物可特异性结合羟基磷灰石并滞留于病变区,增强再矿化定位效率并稳定胶原结构<sup>[70]</sup>;胶原/羟基磷灰石结合双功能肽通过胶原结合域与矿化域协同,在动物模型中有效逆转深部脱矿<sup>[71]</sup>。研究进一步拓展至仿生微环境构建,如基于羟乙酯纤维素、生物活性玻璃与仿生矿化肽QP5(Q-rich and P-rich peptide 5)的复合体系,通过模拟釉质发育的环境,引导晶体有序排列,强化生理性矿化过程,凸显了其在龋病管理中的重要价值<sup>[72-73]</sup>。随着微生态理念成为生物膜管理的核心<sup>[74]</sup>,多肽设计亦由广谱抑菌转向精准调控。pH响应型溶菌肽1(pH-responsive lytic peptide 1, pHly-1)可在酸性环境中被激活并杀灭致龋菌,而在中性条件下自组装为惰性纳米纤维,维持对健康菌群的相容性,实现了对口腔微生物的选择性生态干预<sup>[75]</sup>。该类多肽不仅降低致龋菌

表1 主要抗菌-再矿化-渗透材料的优缺点比较

Table 1 Comparison of advantages and disadvantages of major antibacterial-rem mineralization-infiltration materials

Material category	Representative materials	Key advantages	Main limitations
Antibacterial materials	Silver compounds	Broad-spectrum antibacterial efficacy, long-lasting, well-established history of use	Tooth discoloration, potential cytotoxicity, unclear long-term ecological impact
	Chlorhexidine	Broad-spectrum, highly effective, rapid action	Bitter taste, tooth staining, rapid clearance by saliva, cytotoxic at high concentrations
	Antibacterial peptides	High targeting specificity, low propensity for resistance induction, good biocompatibility	Poor <i>in vivo</i> stability, susceptible to proteolysis, high synthesis cost
	Antibacterial photodynamic therapy	Effective biofilm eradication, non-invasive, low resistance risk	Requires light activation for efficacy, limited penetration depth, non-selective against commensal bacteria
Remineralization materials	Fluorides	Classically effective, promotes fluorapatite formation, low cost	Surface barrier effect impedes deep lesion repair, toxicity risk at high concentrations
	Bioactive glass	Releases ions to raise local pH, induces mineralization, good biocompatibility	Particle size affects performance; balance needed between reaction rate and longevity
	CPP-ACP	Stabilizes and delivers $\text{Ca}^{2+}/\text{PO}_4^{3-}$ , promotes remineralization of deep lesions, safe	Disordered remineralized crystal structure, mechanical recovery inferior to native tissue
Synergistic/smart materials	Biomimetic peptides/proteins	High biomimeticity, can guide ordered crystal growth, designable functionality	Complex structures, stability and cost are major barriers to clinical translation
	Peptide-based systems	High design flexibility, enables multi-functional integration (e.g., antibacterial + remineralization), capable of targeted and responsive (e.g., pH) action	Susceptible to enzymatic degradation, complex and costly synthesis, scaling up production is challenging
	Multifunctional coatings	Multi-drug synergy, smart controlled release (pH/enzyme/light-responsive), high permeability	Complex composition, potential disparity between <i>in vitro</i> and <i>in vivo</i> behavior, long-term safety requires evaluation
	Nanocomposite systems	Multi-functional integration, interface modification, high customizability	Poor mechanical wear resistance, stability challenges at hydrated interfaces

CPP-ACP: casein phosphopeptide-amorphous calcium phosphate

负荷,也为再矿化与渗透材料在深部病变中的有效作用创造了有利环境。

总体而言,多肽体系已从单一功能分子发展为兼具精准抑菌、胶原稳定、深层矿化与材料协同的综合系统。尽管其高度可设计性展现出广阔前景,但仍面临酶解稳定性差、合成成本高等挑战。未来应着力于通过仿生修饰提升稳定性,开发智能递送系统以延长作用时间,并推进模块化制备工艺以加速临床转化。

5.1.2 多功能涂层 薄膜涂层策略的核心是将抗菌、再矿化功能整合于纳米级界面,以阻断菌斑-脱矿的进一步发展。Chu等<sup>[76]</sup>合成了聚乙二醇-聚天冬氨酸-阿仑膦酸盐[poly(ethylene glycol)-b-poly(aspartic acid)-alendronate sodium, PEG-PAsp-ALN]三嵌段聚合物,其中PEG链通过空间位阻抑制蛋白质与细菌黏附,而PAsp与ALN则通过多重配位键锚定于釉质表面并诱导羟基磷灰石沉积。

该涂层在7 d内可使酸蚀釉质显微硬度恢复90%以上,展现出优异的抗污-矿化双功能特性,但其缺乏直接杀菌能力,对成熟生物膜的干预效果有限。

针对上述不足,Lu等<sup>[4]</sup>构建了转变牛血清白蛋白-奥替尼啶复合涂层,利用奥替尼啶的阳离子杀菌作用与白蛋白的模板矿化功能实现协同效应。该涂层可在30 min内在多种基底上形成约130 nm的致密纳米膜,不仅抑制变异链球菌生物膜形成,还能显著提升脱矿釉质硬度,动物实验进一步证实其可有效降低继发龋发生率。Chen等<sup>[77]</sup>则设计了一种仿生超疏水纳米颗粒,其通过羧基-钙螯合牢固锚定于釉质表面,构建接触角>150°的超疏水屏障,在不影响口腔菌群多样性的前提下,将大鼠光滑面龋Keyes评分从3.8显著降至1.2,展现了优异的龋病治疗效果。

除合成材料外,天然多酚类提取物因其多靶

点作用与生物可降解性受到关注<sup>[78]</sup>。Xu等<sup>[79]</sup>发现土耳其栳子提取物可在釉质表面形成亲水薄膜,通过多酚羟基与釉质成分的分子间作用诱导类釉柱结构定向生长,同时破坏致龋菌细胞膜并下调炎症因子表达。动物实验显示,经该提取物处理7 d后,釉质表面可形成25  $\mu\text{m}$ 矿化层,其硬度恢复至天然釉质的149%。

尽管涂层材料前景广阔,其实际应用仍面临机械耐磨性、口腔流体冲刷及表面润湿性稳定性等挑战。未来研究应致力于开发与牙体组织形成稳健结合的类生物界面,以及具备周期性再生能力的动态响应型涂层系统,推动该策略从被动防护向智能响应方向发展。

**5.1.3 纳米复合体系** 纳米复合体系通过智能响应机制为龋病管理提供了新策略。Xu等<sup>[80]</sup>开发了pH响应型仿生胶束系统,其中唾液获得性膜多肽介导牙面特异性黏附,当局部pH降至5.0以下时胶束裂解释放单宁酸与氟化钠,实现按需抗菌。Shi等<sup>[81]</sup>进一步设计出光响应型酪蛋白磷酸肽-自组装肽修饰的肽树枝状大分子纳米凝胶,该凝胶通过SAP序列在釉质表面形成稳定黏附,24 h保留率超过75%,经665 nm激光照射后产生活性氧,清除99%变形链球菌,随后凝胶作为模板诱导原位再矿化,为日常漱口场景下的龋病防控提供了新方案。

在促进矿化方面,Zhi等<sup>[82]</sup>利用富含 $\beta$ -折叠结构的丝素蛋白稳定无定形磷酸钙,结合苯扎氯胺构建的纳米复合体系,能在脱矿釉质表面形成类天然釉质的矿化屏障并展现广谱抗菌性。针对混合生物膜感染,Luo等<sup>[83]</sup>采用焦磷酸修饰脂质体共递送厚朴酚与氟康唑,该体系可靶向羟基磷灰石并在酸性微环境中释放药物,显著提升釉质力学性能与矿化密度。

尽管纳米复合体系通过pH触发、光触发等机制实现了抗菌-再矿化协同作用,但其多组分复杂结构在真实口腔环境中仍面临挑战:唾液冲刷、食物残渣及局部pH波动可能影响载体稳定性与释放行为,导致体外与体内效果存在差异。未来需进一步优化体系的稳定性和响应特异性,以推动其临床转化。

## 5.2 协同策略在非龋性牙体硬组织疾病中的应用

非龋性牙体硬组织疾病(如牙本质敏感、楔状缺损和酸蚀症)虽病因与龋病不同,但其病理基础同样涉及牙体组织缺损以及可能伴随的微生物感

染风险。传统的脱敏剂或充填材料功能单一,难以同时解决多重问题。抗菌-再矿化-渗透协同策略的出现,为这类疾病的综合防治提供了新思路。

**5.2.1 牙本质敏感** 牙本质敏感的病理基础是牙本质小管开放导致的流体动力学刺激。其治疗需兼顾即刻封闭与长期再矿化,以恢复组织强度并降低复发风险。生物活性玻璃(BAG)等钙磷离子释放材料已积累较多临床证据,随机对照试验表明,其牙膏、凝胶或涂层制剂可在中短期内显著缓解敏感,其机制涉及管口矿物封闭、抗酸能力提升及小管内再矿化的多重效应<sup>[84-85]</sup>。

对于再矿化能力受限者,低黏度树脂渗透可提供即时小管封闭。研究显示,树脂经酸蚀后可有效渗入牙本质表层并快速缓解症状<sup>[86]</sup>,当前研究趋向于将再矿化与渗透策略结合,形成“先促矿化后渗透”或“在树脂中掺入活性填料”两类路径。前者通过BAG、CPP-ACP等预处理提升表层性能,以增强后续树脂结合;后者则将BAG、纳米级羟基磷灰石或抗菌纳米颗粒直接分散于树脂中,实现封闭与持续离子释放的协同。临床研究初步表明,含BAG粘接剂在敏感控制方面优于传统处理<sup>[87]</sup>;而抗菌添加虽在体外有效抑制菌载并延缓界面降解<sup>[88]</sup>,但其长期生态影响与力学性能仍需审慎评估。

为克服传统封闭深度不足的局限,相转变溶菌酶纳米膜展现出显著优势,相转变溶菌酶纳米膜能够渗透并黏附于脱矿的牙本质小管内壁中并实现再矿化,在牙本质小管内可形成超过60  $\mu\text{m}$ 的深层矿化层,并有效抑制获得性膜与细菌的附着<sup>[5]</sup>。类似地,基于乳铁蛋白的相转变仿生矿化方法同样可诱导深层羟基磷灰石沉积<sup>[59]</sup>,进一步验证了相转变蛋白质介导的仿生矿化在深化封闭效果方面的潜力。

牙本质敏感的治疗不仅需要即时效果,还需解决长期可能发生的小管再开放、胶原基质持续暴露等问题<sup>[89]</sup>。若矿化深度不足或矿物稳定性不佳,都可能导致敏感复发。因此,后续研究重点应聚焦于:①提升矿物晶体在小管内的长程定向生长能力;②结合抗酶解成分保护胶原基质;③构建即刻封闭-缓释矿化-持续抗菌的三阶段材料体系。这种由短期到长期的梯度调控,是提高治疗效果持久性的关键。

**5.2.2 楔状缺损** 楔状缺损是刷牙磨损和咬合力集中等共同作用导致的长期累积结果,故治疗

时需综合考虑缺损形态、材料力学性能及咬合负载等多重因素,单一的再矿化或封闭修复往往难以实现长期稳定的治疗效果<sup>[90]</sup>。研究者提出了分层管理的理念:对于早期、活动性较低且以敏感为主的楔状缺损,可优先采用再矿化与行为干预;而对有美观、功能需求或结构缺损较深的病变,则往往需要结合粘接修复<sup>[91]</sup>,并将再矿化与抗菌渗透作为充填修复前的辅助手段,以优化边缘适配与延长修复寿命<sup>[92]</sup>。近年来关于协同策略的研究主要集中在两个方面:一是利用多肽、BAG或CPP-ACP等材料对缺损表面进行再矿化,以改善粘接基底与增加表面硬度<sup>[7]</sup>;二是使用低黏度渗透剂或改性粘接剂在修复前或修复时封闭微孔隙,并携带生物活性微粒以实现持续的离子释放<sup>[93]</sup>。体外与动物实验显示,多肽引导的再矿化可促进修复体边缘的再矿化与界面稳定<sup>[94]</sup>;初步临床研究亦表明,术前再矿化处理可以提高随后的复合树脂的粘接质量,并降低术后敏感的发生率。

楔状缺损的治疗目标不仅是缓解敏感,还需实现边缘封闭与结构恢复。协同策略在充填修复前使用时可增强基底硬度、改善粘接界面;术后应用也有助于边缘再矿化与降低二次脱敏风险。然而,由于楔状缺损多与长期机械磨耗与应力集中相关,材料应用后都必须承受远高于龋病区域的机械负荷,若再矿化或渗透后的界面无法抵抗应力,长期耐久性仍将受限。

**5.2.3 酸蚀症** 酸蚀症以化学性矿物溶解为主,常见于胃酸反流、频繁摄取酸性饮料或职业性酸暴露等情况<sup>[95]</sup>。酸蚀导致表层钙磷流失,常伴随表面变薄与晶体结构破坏。再矿化策略在体外与部分临床研究中被证明能部分恢复表面矿物并提高耐酸性;但与牙本质敏感或初期白斑不同,酸蚀病变往往涉及更广泛的表层重构,单次离子释放难以完全重建有序晶体结构。因此,多数学者主张将再矿化作为长期管理与病因控制的一部分<sup>[96]</sup>,在需要恢复美观或结构时,结合微创或传统修复手段。

渗透树脂在酸蚀病变中的应用受限于基底硬度与渗透深度:严重酸蚀的釉质、牙本质,其微孔结构与有机基质破坏会影响渗透剂的黏附与稳定性。因此,更合理的临床路径常为先矿化再考虑粘接修复<sup>[97-98]</sup>。近年来,有研究将BAG或其他生物活性微粒整合入粘接体系,以期在高渗透的同时提供持续再矿化能力<sup>[50]</sup>;早期体外结果显示,这

能提高表面硬度并减少后期酸侵蚀的深度进展,但其长期临床效果仍有待验证。值得注意的是,酸蚀环境下口腔pH的剧烈波动对材料的释放动力学与界面化学稳定性构成了挑战,因此任何协同体系都要在模拟生理或病理pH循环的条件下进行验证<sup>[99]</sup>。未来研究应重点探索能与酸性环境动态响应的耐酸涂层与矿化体系以及开展长期随访研究,明确酸蚀症管理的可逆性界限。推动酸蚀症治疗由恢复表面矿物向重建釉柱结构过渡。

总体而言,抗菌-再矿化-渗透协同策略在各类牙体硬组织疾病中的应用效果,受到病变结构特征、局部微生态状况以及力学环境因素的综合调控。在早期龋损中,该策略侧重于对深部脱矿区域的精准再矿化干预;对于牙本质敏感,则依赖于牙本质小管的有效封闭与深层矿化过程的协同促进;而在楔状缺损及酸蚀症的治疗中,其效果更依赖于材料与牙体组织间的高稳定性界面结合与优良的耐磨耗性能。随着口腔医学领域精准化与微创化理念的深入推进,该协同策略有望在更为系统完善的临床验证体系支撑下,实现从基础研究向临床应用的成功转化。

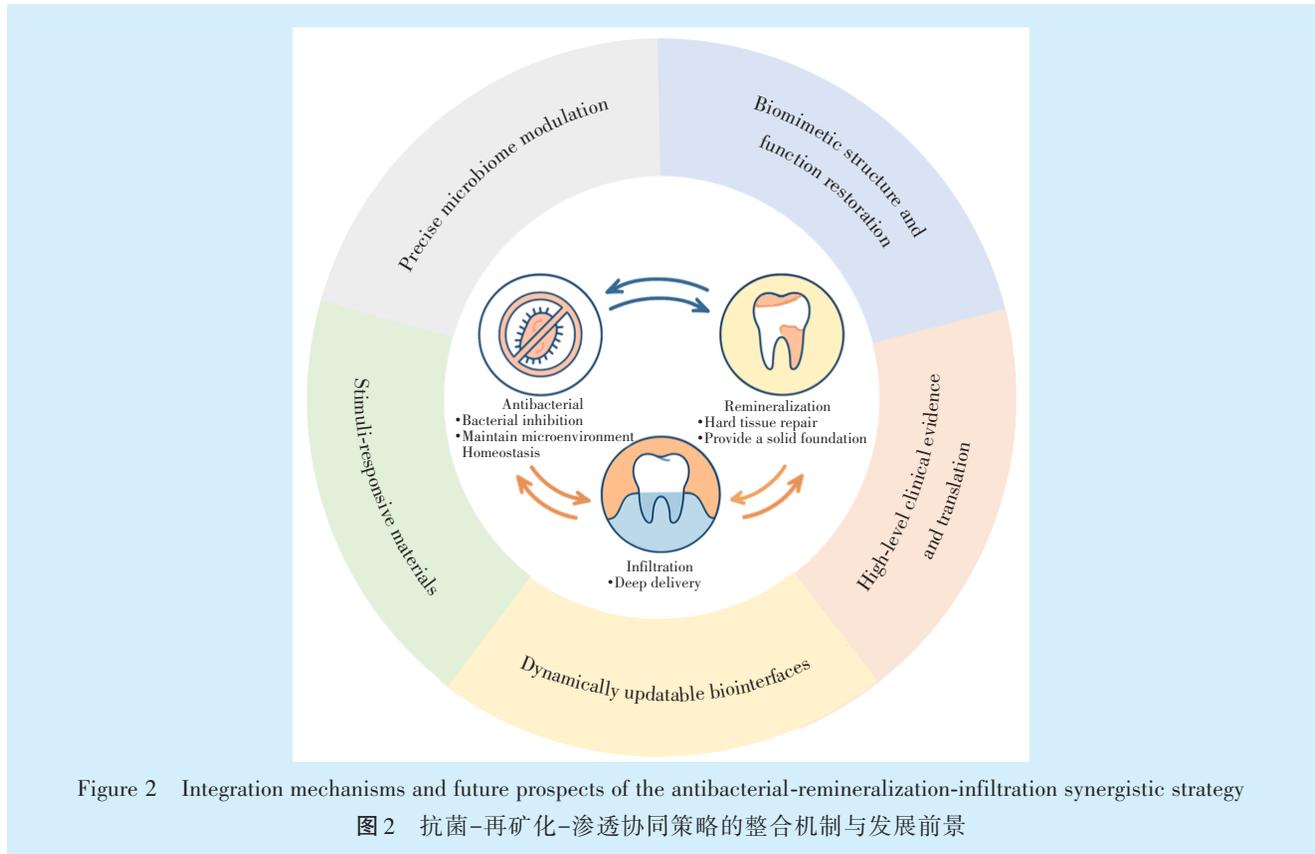
## 6 展望

尽管抗菌-再矿化-渗透协同策略在实验研究中展现出良好的局部抗菌、深层渗透与结构重建潜力,但根据牛津证据等级,目前相关证据仍主要集中于牛津证据等级的4~5级,即体外实验、动物模型及机制性推断为主,高质量临床证据有限。口腔微生态具有高度动态性,受pH波动、生物膜更新与机械磨耗影响显著,导致材料的渗透效率、控释行为及界面稳定性在真实环境中常与体外表表现存在偏差。因此,现阶段协同策略的临床推广仍受到以下局限:①智能控释系统对酸性或酶学信号的响应性能,在不同个体口腔条件下稳定性不足;②仿生矿化体系虽可诱导羟基磷灰石沉积,但在晶体取向重建与深层渗透方面仍难以完全模拟天然组织;③长期抗菌策略对口腔微生态稳态的影响尚缺乏2级以上证据的临床研究支持。

在未来,抗菌-再矿化-渗透协同策略的发展应从功能叠加向系统调控过渡,重点在于提升材料在真实口腔环境中的可预测性与长期稳定性。在临床转化过程中,研究需逐步提升证据等级。应建立更贴近口腔真实环境的微生态模型,以获得更高外推性的前临床证据。随后,开展小样本

临床可行性研究与队列研究,形成2~3级别的证据基础,明确不同材料在早期龋、根面龋与非龋性病变中的适应证。最终,应推动多中心随机对照试验和超过2年的随访研究,以获得1~2级的高证据等级结果,真正支持抗菌-再矿化-渗透协同策略在临床的常规应用(图2)。

总之,随着智能控释、仿生矿化与界面工程技术的持续进步,并在更完善的科学证据基础上,抗菌-再矿化-渗透协同策略有望实现从基础研究向临床应用的转化,从而为牙体硬组织疾病的微创管理提供更为可靠与可持续的治疗路径。



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**【通信作者简介】** 张旭,教授,博士生导师,国家重点研发计划项目首席科学家,国际牙医学院院士(Fellow),中华口腔医学会口腔材料学专业委员会常务委员。长期从事仿生矿化与口腔硬组织修复研究,建立了两性聚电解质仿生矿化体系,提出有机基质自组装与矿化协同进行模式,系统阐释了生物矿化过程中的三个“关键事件”:釉原蛋白模板与非釉原蛋白协同稳定无定形磷酸钙,实现其在时间和空间上的自组装与晶体生长调控;成熟期有机基质的酶解与清除;成熟后期无定形磷酸钙向羟基磷灰石晶体的转化,最终完成矿化过程,并提出“龋病阻断”理论及相关干预技术。相关研究成果发表在 *Advanced Materials*, *Advanced Functional Materials*, *ACS Nano*, *Journal of Dental Research* 等国际材料学和口腔医学领域TOP期刊。获得国家发明专利12项,其中2项实现成果转化;获得省部级科技奖5项,取得二类医疗器械产品注册证1项,参与发表专家共识1篇。