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肠球菌潜在风险

——耐药基因储存库

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摘　要

肠球菌是一种广泛存在于自然环境中的乳酸菌(LAB)，同时也可寄居于人和动物的肠道内。其被认为是引起院内感染的重要条件致病菌，可以引起尿路感染、脑膜炎、心内膜炎和脓毒血症等多种感染性疾病，且其发病率呈现出增高趋势。更重要的是，近年来研究表明，肠球菌可能是耐药基因的储存库，因其固有抗生素耐药性及其迅速获得额外抗生素耐药性的能力使感染很难治疗，尤其是万古霉素耐药菌的出现，构成了重大的感染控制负担。本文就肠球菌的致病性及耐药特性进行综述。

关键词

肠球菌，条件致病菌，耐药性，耐万古霉素

Potential Risks of Enterococci

—Reservoir of Drug-Resistant Genes

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Abstract

Enterococci are ubiquitous lactic acid bacteria (LAB) that exist widely in the natural environment, and they can also reside in the gastrointestinal tract of humans and animals. They are considered as important opportunistic pathogen causing nosocomial infection, and can cause many infectious diseases such as urinary tract infection, meningitis, endocarditis and sepsis. Moreover, the inci-

dence of infectious diseases caused by Enterococci shows an increasing trend. More importantly, studies in recent years have shown that enterococci may be a repository for drug resistance gene, as their inherent antibiotic resistance and their ability to rapidly acquire additional antibiotic resistance make infections much more difficult to treat, particularly the emergence of vancomcin-resistant bacteria, which constitutes a significant burden of infection control. The pathogenicity and drug resistance of enterococcus were reviewed in this paper.

Keywords

Enterococcus, Opportunistic Pathogens, Drug Resistance, Vancomycin Resistance

1. 引言

肠球菌是革兰氏阳性、兼性厌氧、无芽孢形成的乳酸菌(LAB)，其主要存在于人和动物的胃肠道，但也广泛分布于食物和环境中。目前的研究表明，改菌种常常于多种人类疾病的病因学相关，如菌血症、心内膜炎和尿路感染(UTI)，而且肠球菌是引起革兰氏阳性相关菌血症的第二大原因[1]。肠球菌的感染主要由粪肠球菌和屎肠球菌引起，且屎肠球菌的比例不断上升[2]。此外，最近许多研究表明，多重耐药肠球菌尤其是耐万古霉素菌株，它们获得和转移耐药基因和毒力因子的能力都有惊人的增加[3]。本文就场球菌的致病性及其耐药特性进行综述。

2. 肠球菌的分类

肠球菌是一种低 GC 革兰氏阳性卵球菌，可以形成不同长度的链和对。肠球菌属的细菌是过氧化氢酶和氧化酶阴性的兼性厌氧细菌[4]。目前，该属由 58 个物种组成[5] [6] [7]，最近也发现了一些新的物种，比如 *E. thailandicus* [8]、*E. saigonensis* [9]、*E. wangshanyuanii* [6]等。这些物种普遍存在于自然界中，且动物的胃肠道被认为是肠球菌的最大储存库。

3. 条件致病菌肠球菌

近年来由粪肠球菌和屎肠球菌引起的感染性疾病越来越难以治疗[10] [11]，尤其是多重耐药菌和耐万古霉素的肠球菌的出现[12] [13]，因此人们对肠球菌的安全性越来越重视。肠球菌作为机会性病原体的出现主要归因于抗生素耐药性的增加以及几个毒力决定因素的存在。

3.1. 肠球菌毒力因子

毒力因子是增强微生物致病能力的效应分子。肠球菌的毒力因子在肠球菌的致病性中发挥着重要作用。肠球菌常见的毒力决定因素主要分为三类，分别是分泌型毒力因子(细胞溶血素 *Cyl* [14]、明胶酶 *GelE* [15])、细胞表面相关毒力因子(聚集物质 *agg/asa1* [16]、细胞外表面蛋白 *esp* [17]、粘附胶原蛋白 *ace/acm* [10]、粘附样心内膜炎抗原 *efaAfs/efaAfm* [18])和磷酸转移酶系统作为毒力因子。

3.1.1. 分泌型毒力因子

细胞溶血素(*Cyl*)是肠球菌中最早发现也是研究最多的毒力因子[14]。细胞溶血素是具有蛋白质细菌

素/溶血素双功能的肽类毒素，破坏宿主细胞膜促进感染。明胶酶是由 *GelE* 基因编码，是一种胞外锌金属内肽酶，可以水解明胶、胶原、*β*-胰岛素、血红蛋白等生物活性肽[15]。明胶酶能够通过裂解纤维蛋白，破坏宿主组织，从而允许细菌的迁移和扩散，增强了粪肠球菌的毒力[19]。同时，明胶酶在生物膜的形成中起着重要作用，而生物膜允许肠球菌在组织中定植并在某些感染部位持续存在[15]。而且 *GelE* 还被证明可以抑制补体介导的免疫反应[20]。

3.1.2. 细胞表面相关毒力因子

聚集物质(*agg* 和 *asa1*)是一种肠球菌表面蛋白，在肠球菌与宿主组织的粘附中发挥作用,这是许多感染和随后的疾病发展的第一步，同时促进携带毒力特征和抗生素耐药基因质粒的交换[16]。细胞外表面蛋白(*esp*)有助于细胞间粘附，尤其是与真核细胞的粘附和逃避宿主免疫反应有关[17]。*Esp* 在实验性心肌内膜炎的发病机制中起重要作用,同时通过显著增加尿道细胞定植和UTI持久性而参与UTI的发病机制[21]。粪肠球菌和屎肠球菌的胶原粘附基因 *ace* 和 *acm* 与Ⅰ型和Ⅳ型胶原增强毒力菌株结合。*ace* 和 *acm* 促进生物膜形成，参与尿路感染和心肌内膜炎发生机制[10]。粘附样心内膜炎抗原 efaA 毒力基因与心内膜炎密切相关，常见存在于粪肠球菌和屎肠球菌的 *efaAfs* 和 *efaAfm* [19]。

3.2. 肠球菌的耐药性

只有毒力因子的普遍存在并不能解释肠球菌在疾病发展中的作用，对临床相关抗生素广泛耐药也是肠球菌致病性增强引起院内感染的重要原因。近年来，在人类和兽医药物中，过度使用和误用抗生素已经导致肠球菌对多种不同类别的抗生素产生耐药性，严重阻碍肠球菌感染的医疗，进而增加公共卫生的负担。肠球菌通常可以通过靶标修饰、影响药物接近靶标的改变或酶药物灭活来产生抗生素耐药性。

肠球菌对几种抗生素具有固有耐药性，包括头孢菌素、*β*-内酰胺类、磺胺类、氨基糖苷类和半合成青霉素，如苯唑西林[17]。肠球菌对氯霉素、红霉素、氟喹诺酮类、四环素、青霉素、氨苄青霉素、氨基葡萄糖苷(庆大霉素、卡那霉素、链霉素)和糖肽(替考拉宁和万古霉素)也有获得性耐药[4]。获得抗药性基因通常是通过使用信息素响应质粒、接合质粒或可能携带多个抗生素耐药基因的结合转座子来实现[22]。

3.3. 耐万古霉素肠球菌(VRE)

万古霉素耐药性受到极大重视是因为由耐万古霉素肠球菌引起的严重感染和疾病不能用常规的抗生素治疗[23]。VRE 同时也给临床医生带来巨大挑战，因为万古霉素传统上被认为是治疗肠球菌感染的最后药物，经常用于替代青霉素、氨苄青霉素和氨基糖苷类药物治疗过敏患者。根据世界卫生组织(WHO)，耐万古霉素肠球菌是需要紧急开发抗菌药物的微生物名单中高优先级别的病原菌[24]。因此，正在对新药进行评估以取代万古霉素包括半合成糖肽、利奈唑胺、达托霉素和替加环素[25]。

万古霉素是一种糖肽类抗生素，它通过与交联肽聚糖的肽链的 D-丙氨酸-D-丙氨酸(D-ALA-D-ALA)部分结合来防止肽聚糖的交联。当肽聚糖前体的末端氨基酸由 D-丙氨酸-D-丙氨酸(D-Ala-D-Ala)改变为 D-丙氨酸-D-乳酸(D-Ala-D-Lac)或 D-丙氨酸-D-丝氨酸(D-Ala-D-Ser)时，肠球菌对万古霉素产生抗性，从而分别产生高水平和低水平的万古霉素抗性。目前已知有 9 个基因簇与肠球菌对万古霉素耐药有关。这些万古霉素抗性基因簇是通过形成 D-丙氨酸-D-乳酸(D-Ala-D-Lac)的 VanA、vanB、VanD 和 vanM，和催化形成 D-丙氨酸-D-丝氨酸(D-Ala-D-Ser)的 vanC、VanE、VanG、VanL 和 VanN 而产生万古霉素抗性[25] [26] [27] [28]。

在粪肠球菌和屎肠球菌中，*vanA* 和 *vanB* 基因基因簇最常见，并且可以水平和垂直转移，因此被认为是糖肽耐药方面最重要的临床基因簇[17]。在欧洲和美洲国家进行的几项研究报告说，除了人类库以外，VRE 在社区中也存在；动物、环境和食物库也可以作为卫生保健环境之外的 VRE 的社区来源[29]。VRE

可通过不同来源的环境污染、污水处理废水、牲畜粪便和家禽养殖场的粪便进入食品[29]。此外，在世界各地的食用动物和环境中也发现了其他具有抗药性的肠球菌。在所有这些不同的储存库和环境中出现这种高抗药性表明抗药性基因在菌株间普遍传播。

4. 展望

自然界中大多数的肠球菌可能并不致病，但是却是院内感染肠球菌群的基因库。肠球菌具有极强的毒力因子转移能力，减少毒力因子的转移尤其是屎肠球菌，可以大大降低肠球菌耐药性产生的速度。因此，在人医和兽医中应该更加谨慎使用抗生素，另外选择其他药物代替抗生素刺激禽类生长。还应严格控制环境和食物来源中是否存在肠球菌，以防止或限制致病性肠球菌菌株的传播。

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