·论　著·

无乳链球菌对奥马环素的敏感性研究

邹凡路[1]，施逸怡[1]，余治健[1]，潘伟光[2]，王红燕[1]，程航[2]，邓向斌[1*]，熊焱鹏[2*]

1. 广东医科大学医学院附属深圳市南山区人民医院，广东 深圳 518052；
2. 深圳市内源性感染诊治研究重点实验室，广东 深圳 518052

摘要：目的　研究无乳链球菌（*Streptococcus agalactiae*, GBS）对奥马环素（omadacycline, OMC）的药敏特点及其与生物被膜形成能力、耐药基因、毒力基因之间的关系。**方法**　收集深圳市南山区人民医院2015—2020年无乳链球菌临床分离株共136株，用微量肉汤稀释法测定这些菌株对OMC的最小抑菌浓度（minimum inhibitory concentration, MIC），用结晶紫染色法检测无乳链球菌的生物膜，采用聚合酶链反应（PCR）方法检测耐药基因（*tet*M、*tet*O、*tet*K、*erm*B、*Optr*A）和毒力基因（*cps*Ⅲ、*bca*、*fbs*A、*cps*A、*scp*B）。**结果**　136株临床分离的无乳链球菌中，对OMC耐药的有20株（14.7%），中介有64株（47.1%），敏感有52株（38.2%）；生物被膜阳性菌株有57株（41.9%），对OMC敏感的有20株（35.1%），生物被膜阴性菌株有79株（58.1%），对OMC敏感的有32株（40.5%），两组菌株敏感率之间差异有统计学意义（χ^2=63.062，*P*<0.001），但生物被膜阳性菌株组间对OMC的敏感性差异无统计学意义（Fisher确切概率法，*P*=0.824）。*tet*M、*tet*O、*erm*B、*Optr*A耐药基因阳性菌株耐药率均高于阴性菌株，*tet*K耐药基因阳性菌株耐药率低于阴性菌株，无乳链球菌是否有耐药基因*tet*M（*Z*=0.815，*P*=0.415）、*tet*O（*Z*=0.151，*P*=0.88）、*tet*K（*Z*=0.567，*P*=0.571）、*erm*B（*Z*=1.198，*P*=0.231）均对OMC敏感性影响差异无统计学意义，而是否有耐药基因*Optr*A对OMC敏感性影响差异有统计学意义（*Z*=2.913，*P*=0.004）。毒力基因*cps*Ⅲ、*bca*、*fbs*A、*cps*A、*scp*B携带率均>50%，无乳链球菌是否有毒力基因*cps*Ⅲ（*Z*=0.222，*P*=0.824）、*bca*（*Z*=0.141，*P*=0.888）、*fbs*A（*Z*=0.813，*P*=0.416）、*cps*A（*Z*=1.615，*P*=0.106）均对OMC敏感性影响差异无统计学意义，而是否有毒力基因*scp*B对OMC敏感性影响差异有统计学意义（*Z*=2.844，*P*=0.004），但是*scp*B阳性菌株的秩均值及耐药率均小于阴性菌株。**结论**　无乳链球菌生物被膜形成降低了对OMC的敏感性，但生物被膜阳性菌株组间对OMC的敏感性无明显差异；无乳链球菌是否存在耐药基因*tet*M、*tet*O、*tet*K、*erm*B和毒力基因*cps*Ⅲ、*bca*、*fbs*A、*cps*A、*scp*B与OMC的耐药无关，但耐药基因*Optr*A的存在与OMC的耐药相关。

关键词：无乳链球菌；奥马环素；生物被膜；毒力基因；耐药基因

中图分类号：R446.5　**文献标识码：**A　**文章编号：**1009-9727(2023)09-966-05

DOI:10.13604/j.cnki.46-1064/r.2023.09.13

Research on the sensitivity of *Streptococcus agalactiae* to omadacycline

ZOU Fanlu[1], SHI Yiyi[1], YU Zhijian[1], PAN Weiguang[2], WANG Hongyan[1], CHENG Hang[2], DENG Xiangbin[1], XIONG Yanpeng[2]

1. Shenzhen Nanshan People's Hospital of Guangdong Medical University, Shenzhen, Guangdong 518052, China; 2. Department of Infectious Diseases and Shenzhen Key Laboratory for Endogenous Infections, Shenzhen, Guangdong 518052, China

Corresponding author: DENG Xiangbin, E-mail: dxblam@163.com; XIONG Yanpeng, E-mail: xyp13726254938@163.com

Abstract: Objective　To investigate the antimicrobial activity of omadacycline (OMC) against clinical *Streptococcus agalactiae* (GBS) isolates, as well as its relationship with biofilm formation, resistance genes and virulence genes. **Methods**　A total of 136 strains of *Streptococcus agalactiae* isolated from Shenzhen Nanshan People's Hospital between 2015 to 2020. The minimum inhibitory concentration (MIC) of OMC against *Streptococcus agalactiae* was determined by broth microdilution. Crystal violet staining was used to detect the biofilm formation ability of GBS. Resistance genes (*tet*M, *tet*O, *tet*K, *erm*B, *Optr*A) and virulence genes (*cps*Ⅲ, *bca*, *fbs*A, *cps*A, *scp*B) were investigated by polymerase chain reaction (PCR). **Results**　Among the 136 clinical isolates of GBS, 20 strains (14.7%) were resistant to OMC, 64 (47.1%) were intermediate, and 52 (38.2%) were sensitive. Fifty-seven strains (41.9%) were biofilm-positive, 20 of which (35.1%) were sensitive to OMC. Seventy-nine strains (58.1%) were biofilm-negative, 32 of which (40.5%) were susceptible to OMC. There was a statistically significant difference in the sensitivity rates between the two groups of strains (χ^2=63.062, *P*<0.001), but there was no significant difference in the sensitivity of OMC among the biofilm-positive strains (Fisher's exact test, *P*=0.824). The resistance rates of *tet*M, *tet*O, *erm*B and *Optr*A positive strains were higher than those of negative strains, while *tet*K was opposite. The presence of *tet*M (*Z*=0.815, *P*=0.415), *tet*O (*Z*=0.151, *P*=0.88), *tet*K (*Z*=0.567, *P*=0.571), *erm*B (*Z*=1.198, *P*=0.231) resistance genes in *Streptococcus*

基金项目：深圳市科技计划项目（No. JCYJ20180302144403714，No. JCYJ20180302144345028）

作者简介：邹凡路（1998—），女，硕士，医师，研究方向：细菌耐药、感染性疾病。

***通信作者：**邓向斌，E-mail: dxblam@163.com；熊焱鹏：E-mail: xyp13726254938@163.com

agalactiae had no significant impact on the sensitivity of OMC. However, the presence of the *Optr*A resistance gene showed a statistically significant effect on the sensitivity of OMC (Z=2.913, P=0.004). The virulence factors *cps* Ⅲ, *bca*, *fbs*A, *cps*A and *scp*B were all detected at a rate higher than 50%. The presence of the virulence genes *cps* Ⅲ (Z=0.222, P=0.824), *bca* (Z=0.141, P=0.888), *fbs*A (Z=0.813, P=0.416), and *cps*A (Z=1.615, P=0.106) in *Streptococcus agalactiae* had no significant impact on the sensitivity of OMC. However, there was a significant inter-group difference in the *scp*B virulence gene (Z=2.844, P=0.004), but the rank mean values and resistance rates of *scp*B-positive strains were lower than those of the negative strains. **Conclusions** The formation of biofilm in *Streptococcus agalactiae* reduces its sensitivity to OMC, but there was no significant difference in the sensitivity to OMC among the biofilm-positive strains. The presence of resistance genes *tet*M, *tet*O, *tet*K, *erm*B, and virulence genes *cps* Ⅲ, *bca*, *fbs*A, *cps*A, *scp*B in *Streptococcus agalactiae* is not associated with OMC resistance, but the presence of the resistance gene *Optr*A is correlated with OMC resistance..

Keywords: *Streptococcus agalactiae*; omadacycline; biofilm; virulence genes; resistance genes

无乳链球菌(*Streptococcus agalactiae*, GBS)又称B组链球菌,是一种兼性厌氧的革兰阳性球菌,广泛存在于大自然中,也可定植于人体的生殖道及消化道[1],尤其是女性,是引起孕妇及新生儿感染性疾病的重要病原体[2-4]。治疗无乳链球菌感染的常用抗菌药物,如青霉素、红霉素、克林霉素、氧氟沙星,因在临床中广泛使用,导致无乳链球菌对青霉素敏感性降低以及对大环内酯类、喹诺酮类、四环素类抗菌药物耐药率逐年上升[5-8]。

生物膜是细菌为了适应生存环境或抵御抗菌药物而形成的一种存在形式,能帮助细菌抵御外环境变化,躲避机体免疫清除、吞噬及抗菌药物杀伤作用。毒力因子常与细菌致病能力相关,通过帮助菌体黏附与侵袭细胞、菌体释放毒素和逃避宿主免疫应答等产生感染。分析当地无乳链球菌主要致病毒力因子,针对其开发疫苗,有利于减少感染事件发生。耐药基因通过表达蛋白对抗抗菌药物的杀菌或抑菌机制,从而使细菌产生耐药。研究细菌所具有的耐药基因,可给临床选择敏感抗菌药物提供参考。

奥马环素(omadacycline, OMC)是一种新型广谱四环素类抗菌药物,对各种细菌和非典型病原体均有效,美国食品药品监督管理局(Food and Drug Administration, FDA)已经批准其用于治疗成人社区获得性肺炎和由敏感微生物引起的成人急性细菌性皮肤感染[9-10]。但OMC对无乳链球菌的抗菌活性如何,无乳链球菌常见的耐药基因、毒力基因是否会导致其对OMC耐药率增加,这些问题在之前的临床研究中少有报道。本实验主要研究无乳链球菌的生物被膜形成能力、耐药基因及毒力基因对OMC敏感性的影响,阐述它们之间的关系。

1 材料和方法

1.1 材料

1.1.1 细菌菌株 菌株来源于深圳市南山区人民医院2015—2020年患者的尿液、血液、羊水、痰、胃液、脑脊液以及阴道、尿道、伤口分泌物等标本,从中分离出136株无乳链球菌菌株,无重复患者菌株,质控菌株是肺炎链球菌ATCC49619菌株、粪肠球菌OGRF菌株和CHS787菌株。

1.1.2 奥马环素 购买于MedChemExpress(MCE,上海,中国)。

1.2 方法

1.2.1 菌株鉴定、药敏试验及最低抑菌浓度(Minimum inhibitory concentration, MIC) 无乳链球菌的鉴定及OMC药敏试验采用VITEK 2 Compact全自动细菌鉴定及药敏分析系统(法国梅里埃公司),使用微量肉汤稀释法测定OMC的MIC值,以肺炎链球菌ATCC49619作为质控菌株,参照2020年美国临床和实验标准化协会指南(Clinical and Laboratory Standards Institute, CLSI)[11]及文献[12],判定OMC的MIC折点:敏感≤0.25 mg/L、中介0.5 mg/L和耐药≥1 mg/L。

1.2.2 生物膜检测及判读 参考文献[13]方法,采用结晶紫染色法检测无乳链球菌生物被膜的形成。无乳链球菌菌株接种于胰酪大豆胨液体培养基(TSB培养基),在37 ℃摇床中培养过夜,然后将菌液按1∶200稀释于含0.5%葡萄糖的TSB培养基中。将每孔200 μL的培养物加入到96孔板中,每个菌株设置3个复孔,在37 ℃的室温下静态培养24 h。培育结束后,用磷酸盐缓冲液(phosphate buffered saline, PBS)冲洗3次,甲醇固定15 min,再用0.5%结晶紫染色10 min,然后用蒸馏水洗去未结合的结晶紫,最后加入4∶1的无水乙醇和丙酮的混合溶液,混合均匀,在OD_{570}分光光度计下进行测试。粪肠球菌OG1RF和CHS787用作质量控制菌株。结果提示96个微孔中生物被膜的OD_{570}值为0.12~3.09。参考文献[12]的方法判读生物膜OD_{570}值并进行分类,以0.5为折点,分为生物被膜阳性和阴性组,生物被膜阳性组再以OD_{570}值分为生物被膜形成能力强、中、弱3组:强阳性(OD_{570}值>2)、中等(1<OD_{570}值≤2)和弱阳性(0.5<OD_{570}值≤1)。

1.2.3 无乳链球菌耐药基因和毒力基因检测 由北京六合华大基因公司合成耐药基因(*tet*M、*tet*O、*tet*K、*erm*B、*Optr*A)和毒力基因(*cps*Ⅲ、*bca*、*fbs*A、*cps*A、*scp*B)引物(表1)。将菌株分别于TSB培养液中进行过夜培养,然后按DNA提取试剂盒(Invitrogen)说明书步骤提取DNA,采用聚合酶链反应(PCR)反应扩增基因,反应产物均用1%的琼脂糖凝胶电泳检测分析无乳链球菌耐药基因及毒力基因。

表1 无乳链球菌耐药基因及毒力基因的引物序列

Table 1 Primers sequence of resistance gene and virulence gene of *Streptococcus agalactiae*

基因 Gene	引物 Primer	引物序列(5′→3′) Primer sequence (5′→3′)
*tet*M	*tet*M-F	CAATACAATAGGAGCAAGC
	*tet*M-R	CGAACAAGAGGAAAGCATAAG
*tet*O	*tet*O-F	AACTTAGGCATTCTGGCT CAC
	*tet*O-R	TCCCACTGTTCCATATCGTCA
*tet*K	*tet*K-F	TCGATAGGAACAGCAGTA
	*tet*K-R	CAGCAGATCCTACTCCTT
*erm*B	*erm*B-F	CCGTTTACGAAATTGGAACAGGTAAAGGGC
	*erm*B-R	GAATCGAGACTTGAGTGTGC
*Optr*A	*Optr*A-F	AGGTGGTCAGCGAACTAA
	*Optr*A-R	ATCAACTGTTCCCATTCA
*cps*Ⅲ	*cps*Ⅲ-F	TCCGTACTACAACAGACTCATCC
	*cps*Ⅲ-R	AGTAACCGTCCATACATTCTATAAGC
bca	*bca*-F	TAACAGTTATGATACTTCACAGAC
	bca-R	ACGACTTTCTTCCGTCCACTTAGG
*fbs*A	*fbs*A-F	GAACCTTCTTGTCACACTTG
	*fbs*A-R	TTGATCCTAGCACTCCCA
*cps*A	*cps*A-F	ACAACGCTTCACTGTCGAGTCAC
	*cps*A-R	AGCTCCTGGCATTGCATATGAAGG
*scp*B	*scp*B-F	AGCCATATGCTGCGATCTCT
	*scp*B-R	GGGTTGAACCAAGTGTGCTT

1.2.4 统计学分析 采用SPSS 26.0软件进行数据统计分析,计数资料以例数n和率/构成比(%)表示。比较组间率或构成比差异时采用χ^2检验;当样本量较小,即存在预测频数小于5时,采用Fisher确切概率法;比较组间平均水平或总的程度时采用秩和检验。均为双侧检验,以$P<0.05$为差异有统计学意义。

2 结 果

2.1 无乳链球菌生物被膜形成能力和奥马环素敏感性之间的关系 生物被膜阳性菌株57株(41.9%),生物被膜阳性菌株对OMC敏感、中介和耐药的分别有20株、30株、7株;对比各组之间的敏感率,阴性组(40.5%)最高,生物被膜强阳性组(22.2%)最低。进一步比较各组MIC值与生物被膜形成能力的相关性,发现生物被膜阳性组较阴性组的敏感性低,差异有统计学意义($\chi^2=63.062$,$P<0.001$);但生物被膜阳性3组之间对OMC的敏感性差异无统计学意义(Fisher确切概率法,$P=0.824$)。见表2。

表2 无乳链球菌生物被膜和奥马环素敏感性之间的关系

Table 2 Relationship between biofilm of *Streptococcus agalactiae* and omadacycline sensitivity

生物被膜 Biofilm	敏感(敏感率/%) Susceptible (Sensitivity rate/%)	中介 Intermediate	耐药 Resistant
阴性 Negative (n=79)	32(40.5)	34	13
阳性 Positive (n=57)	20(35.1)	30	7
弱阳 Weak positive (n=34)	10(29.4)	20	4
中阳 Moderate positive (n=14)	8(57.1)	4	2
强阳 Strong positive (n=9)	2(22.2)	6	1

2.2 无乳链球菌耐药基因与奥马环素敏感性的关系 根据2020年CLSI的标准,检测136株无乳链球菌对OMC的MIC值,其中有52株敏感菌株(38.2%)、有64株中介菌株(47.1%)、有20株耐药菌株(14.7%)。为进一步明确耐药菌株与无乳链球菌耐药基因之间的相关性,检测了136株临床分离株关于四环素类、大环内酯类及利奈唑胺常见部分耐药基因*tet*M、*tet*O、*tet*K、*erm*B、*Optr*A;其中*tet*M阳性60株、*tet*O阳性46株、*tet*K阳性31株、*erm*B阳性98株、*Optr*A阳性13株。结果提示*Optr*A阳性菌株秩均值及耐药率均高于*Optr*A阴性菌株,认为具有*Optr*A基因的无乳链球菌更易对OMC产生耐药($Z=2.913$,$P=0.004$),其余各组耐药基因阳性菌株与阴性菌株对OMC敏感性差异无统计学意义($P>0.05$)。见表3。

2.3 无乳链球菌毒力基因与奥马环素敏感性之间的关系 无乳链球菌毒力基因*scp*B阳性菌株与阴性菌株之间对OMC敏感性差异有统计学意义($Z=2.844$,$P=0.004$),但*scp*B阳性菌株的秩均值及耐药率均小于*scp*B阴性菌株。毒力基因*cps*Ⅲ、*bca*、*fbs*A、*cps*A阳性菌株与阴性菌株之间对OMC敏感性差异无统计学意义($P>0.05$)。见表4。

表3 无乳链球菌耐药基因与奥马环素药敏之间的关系

Table 3 Relationship between resistance genes of *Streptococcus agalactiae* and omadacycline sensitivity

基因 Gene	敏感 Susceptible	中介 Intermediate	耐药(耐药率/%)Resistant (Resistance rate/%)	*Z*	*P*
*tet*M				0.815	0.415
+(*n*=60)	26	25	9(15.0)		
−(*n*=76)	26	39	11(14.5)		
*tet*O				0.151	0.880
+(*n*=46)	19	19	8(17.4)		
−(*n*=90)	33	45	12(13.3)		
*tet*K				0.567	0.571
+(*n*=31)	9	19	3(9.7)		
−(*n*=105)	43	45	17(16.2)		
*erm*B				1.198	0.231
+(*n*=98)	34	49	15(15.3)		
−(*n*=38)	18	15	5(13.2)		
*Optr*A				2.913	0.004
+(*n*=13)	1	7	5(38.5)		
−(*n*=123)	51	57	15(12.2)		

注:+.阳性;−.阴性。Note: +. Positive; −. Negative.

表4 无乳链球菌毒力基因与奥马环素敏感性之间的关系

Table 4 Relationship between virulence gene of *Streptococcus agalactiae* and omadacycline sensitivity

基因 Gene	敏感 Susceptible	中介 Intermediate	耐药(耐药率/%)Resistant (Resistance rate/%)	*Z*	*P*
*cps*Ⅲ				0.222	0.824
+(*n*=79)	32	34	13(16.5)		
−(*n*=57)	20	30	7(12.3)		
bca				0.141	0.888
+(*n*=132)	50	63	19(14.4)		
−(*n*=4)	2	1	1(25.0)		
*fbs*A				0.813	0.416
+(*n*=99)	37	45	17(17.2)		
−(*n*=37)	15	19	3(8.1)		
*cps*A				1.615	0.106
+(*n*=135)	52	64	19(14.1)		
−(*n*=1)	0	0	1(100.0)		
*scp*B				2.844	0.004
+(*n*=126)	51	60	15(11.9)		
−(*n*=10)	1	4	5(50.0)		

注:+.阳性;−.阴性。Note: +. Positive; −. Negative.

3 讨 论

无乳链球菌是健康女性胃肠道和生殖道中的正常菌群,但会引起机会性感染。相关研究指出,无乳链球菌是导致孕妇和新生儿侵袭性感染的首要病原菌[14]。同时该病原菌也易使老年人、免疫力低下的成年人发生感染,主要引起菌血症、皮肤和软组织感染、肺炎等[1]。青霉素是治疗无乳链球菌感染的首选抗菌药物,对青霉素过敏的高风险人群推荐使用四环素类及大环内酯类药物[15]。然而,近些年对这些替代性药物的耐药率在全球范围内呈上升趋势,给无乳链球菌的治疗带来困难[4],为此寻找敏感的新型抗菌药物颇有必要。OMC在2018年经FDA获批上市,对于治疗急性细菌性皮肤和皮肤软组织感染以及社区获得性细菌性肺炎有较好的疗效,药物不良反应小[16-17]。本研究结果提示深圳市无乳链球菌OMC耐药率为14.7%,对比目前国内外传统四环素类药物的高耐药率而言,新型四环素类药物OMC对无乳链球菌具备较高的药物敏感性。

生物被膜形成是导致多种菌株产生耐药性的原因之一,进一步分析无乳链球菌生物被膜形成与OMC的药敏关系,结果提示阴性组的敏感率最高,生物被膜强阳性组的敏感率最低,认为生物被膜的形成会增加OMC耐药率,如在临床使用中疗效不佳,可考虑联用对细菌生物被膜渗透性好的抗菌药物。

多项研究表明,无乳链球菌对四环素类药物常见的耐药机制为药物泵出机制和核糖体蛋白保护机制[18-20],但OMC结构上C7、C9位的修饰能使其克服这两种机制,故而相比于其他四环素类药物,OMC对无乳链球菌存在更好的抗菌活性,可作为耐药菌的备选药物之一。本次研究结果也证实了此结论,*tet*M、*tet*O、*tet*K四环素耐药基因与OMC的MIC值差异无统计学意义。*Optr*A基因常见于对利奈唑胺耐药的菌株[21],本研究提示OMC对具有*Optr*A基因的无乳链球菌更易产生耐药,两者之间是否存在交叉耐药的可能,具体机制有待进一步研究。

无乳链球菌具有许多毒力因子,包括表面定位蛋白、调节蛋白、荚膜多糖、毒素[22],本研究中毒力基因*cps*Ⅲ、*bca*、*fbs*A、*cps*A及*scp*B有帮助细菌粘附并进入宿主细胞、逃避免疫吞噬、促进存活的作用[23],从而增强其致病能力,但本研究结果显示毒力基因*cps*Ⅲ、*bca*、*fbs*A、*cps*A与OMC敏感性之间差异无统计学意

义。虽然是否携带毒力基因*scp*B对OMC敏感性差异有统计学意义，但*scp*B阳性菌株的秩均值及耐药率均小于*scp*B阴性菌株，考虑可能是由于样本数差距较大导致的误差，故认为毒力基因*scp*B与耐药无关。

综上所述，OMC对于深圳地区的无乳链球菌总体较为敏感，在临床上可作为耐药的无乳链球菌菌株的备选抗菌药物之一。但全球的无乳链球菌感染分布情况、耐药性存在明显的地域性差异，本研究数据来自深圳市南山区人民医院136株无乳链球菌，考虑样本数偏少，所得结果仅供参考，结论有待进一步增大样本量再进行分析。

伦理审查与知情同意　本研究不涉及伦理审查与知情同意

利益冲突声明　所有作者声明不存在利益冲突

参考文献

[1] THOMAS L, COOK L. Two-component signal transduction systems in the human pathogen Streptococcus agalactiae[J]. Infect Immun, 2020, 88(7): e00931-19.

[2] PLAINVERT C, HAYS C, TOUAK G, et al. Multidrug-resistant hypervirulent group B Streptococcus in neonatal invasive infections, France, 2007-2019[J]. Emerg Infect Dis, 2020, 26(11): 2721-2724.

[3] ALI M M, WOLDEAMANUEL Y, ASRAT D, et al. Features of Streptococcus agalactiae strains recovered from pregnant women and newborns attending different hospitals in Ethiopia[J]. BMC Infect Dis, 2020, 20(1): 848.

[4] DO NASCIMENTO C S, DOS SANTOS N F B, FERREIRA R C C, et al. Streptococcus agalactiae in pregnant women in Brazil: prevalence, serotypes, and antibiotic resistance[J]. Braz J Microbiol, 2019, 50(4): 943-952.

[5] GUO H W, FU M Z, PENG Q, et al. Antimicrobial resistance and molecular characterization of Streptococcus agalactiae from pregnant women in Southern China[J]. J Infect Dev Ctries, 2019, 13(9): 802-809.

[6] BANNO H, KIMURA K, SEKI T, et al. High isolation rate and multidrug resistance tendency of penicillin-susceptible group B Streptococcus with reduced ceftibuten susceptibility in Japan[J]. Eur J Clin Microbiol Infect Dis, 2018, 37(8): 1511-1519.

[7] WANG X L, CAO X L, LI S M, et al. Phenotypic and molecular characterization of Streptococcus agalactiae colonized in Chinese pregnant women: predominance of ST19/III and ST17/III[J]. Res Microbiol, 2018, 169(2): 101-107.

[8] ESKANDARIAN N, ISMAIL Z, NEELA V, et al. Antimicrobial susceptibility profiles, serotype distribution and virulence determinants among invasive, non-invasive and colonizing Streptococcus agalactiae (group B Streptococcus) from Malaysian patients[J]. Eur J Clin Microbiol Infect Dis, 2015, 34(3): 579-584.

[9] 伍玉琪, 吴安华. 新型四环素类抗生素omadacycline的研究进展[J]. 中国感染控制杂志, 2019, 18(11): 1087-1092. WU Y Q, WU A H. Research progress in omadacycline, a novel tetracycline antibiotic[J]. Chin J Infect Control, 2019, 18(11): 1087-1092.(in Chinese)

[10] BAKER D E. Omadacycline[J]. Hosp Pharm, 2019, 54(2): 80-87.

[11] Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing[S]. 30th ed, CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute, 2020.

[12] LI G Q, WEI Y, GUO Y, et al. Omadacycline efficacy against Streptococcus agalactiae isolated in China: correlation between resistance and virulence gene and biofilm formation[J]. Comput Intell Neurosci, 2022, 2022: 7636983.

[13] PARKER R E, LAUT C, GADDY J A, et al. Association between genotypic diversity and biofilm production in group B Streptococcus[J]. BMC Microbiol, 2016, 16: 86.

[14] PORTA K, RIZZOLO D. Preventing group B streptococcal infections in newborns[J]. J Am Acad Physician Assist, 2015, 28(3): 24-29.

[15] NADEAU H C G, EDWARDS R K. Prophylaxis against early-onset group B Streptococcus infections in pregnant women who are allergic to penicillin[J]. Clin Obstet Gynecol, 2019, 62(4): 771-780.

[16] STETS R, POPESCU M, GONONG J R, et al. Omadacycline for community-acquired bacterial pneumonia[J]. N Engl J Med, 2019, 380(6): 517-527.

[17] ABRAHAMIAN F M, SAKOULAS G, TZANIS E, et al. 1347. omadacycline for acute bacterial skin and skin structure infections: integrated analysis of randomized clinical trials[J]. Open Forum Infect Dis, 2018, 5: S412.

[18] VILLANO S, STEENBERGEN J, LOH E. Omadacycline: development of a novel aminomethylcycline antibiotic for treating drug-resistant bacterial infections[J]. Future Microbiol, 2016, 11(11): 1421-1434.

[19] BUNDRANT L A, TZANIS E, GARRITY-RYAN L, et al. Safety and pharmacokinetics of the aminomethylcycline antibiotic omadacycline administered to healthy subjects in oral multiple-dose regimens[J]. Antimicrob Agents Chemother, 2018, 62(2): e01487-17.

[20] FLUIT A C, VAN GORKUM S, VLOOSWIJK J. Minimal inhibitory concentration of omadacycline and doxycycline against bacterial isolates with known tetracycline resistance determinants[J]. Diagn Microbiol Infect Dis, 2019, 94(1): 78-80.

[21] LIU B G, YUAN X L, HE D D, et al. Research progress on the oxazolidinone drug linezolid resistance[J]. Eur Rev Med Pharmacol Sci, 2020, 24(18): 9274-9281.

[22] UDO E E, BOSWIHI S S, AL-SWEIH N. Genotypes and virulence genes in group B streptococcus isolated in the maternity hospital, Kuwait[J]. Med Princ Pract, 2013, 22(5): 453-457.

[23] BOBADILLA FERNANDO J, NOVOSAK MARINA G, CORTESE ILIANA J, et al. Prevalence, serotypes and virulence genes of Streptococcus agalactiae isolated from pregnant women with 35-37 weeks of gestation[J]. BMC Infect Dis, 2021, 21(1): 73.

收稿日期：2022-11-25　**编辑**：朱学义　王佳燕