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◇药物与临床◇

耐碳青霉烯肺炎克雷伯菌对头孢他啶/阿维巴坦的耐药情况及其危险因素分析

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摘要: 目的 探讨耐碳青霉烯类肺炎克雷伯菌(CRKP)对头孢他啶/阿维巴坦(ceftazidime/avibactam,CZA)的耐药情况及危险因素。**方法** 选取2019年10月至2022年5月在西安国际医学中心重症监护病房(intensive care unit,ICU)住院治疗的CRKP病人156例,根据CRKP病人是否对CZA耐药分为CZA敏感组(n=111)和耐药组(n=45)。采用微量肉汤稀释法检测CRKP对CZA的药敏情况。分析比较CRKP对CZA敏感病人和耐药病人的一般资料,多因素logistic回归分析CRKP对CZA耐药的危险因素。比较两组病人住院期间的死亡率。**结果** 156株CRKP中111株(71.15%)对CZA敏感,45株(28.85%)对CZA耐药。两组病人在年龄、性别、身体质量指数、标本来源和基础疾病上差异无统计学意义(P>0.05)。在侵入性操作中,CZA耐药组机械通气(77.78%比55.86%)、透析(46.67%比18.02%)和手术的病人(77.78%比54.05%)比例明显高于CZA敏感组(P<0.05)。同时,CZA耐药组既往接受CZA治疗的病人比例明显高于CZA敏感组(24.44%比9.01%),差异有统计学意义(P<0.05)。多因素logistic回归分析显示CRKP对CZA耐药的危险因素包括透析、机械通气和既往接受CZA治疗(P<0.05)。CZA耐药组中病人住院期间死亡率(28.89%)明显高于CZA敏感组(10.81%),差异有统计学意义(χ^2=7.78,P=0.005)。**结论** 部分CRKP对CZA耐药,耐药病人住院期间死亡率高。透析、机械通气和既往接受CZA治疗是CRKP对CZA耐药的危险因素。

关键词: 肺炎克雷伯菌; 抗药性,细菌; 耐碳青霉烯肺炎克雷伯菌; 头孢他啶; 阿维巴坦; 危险因素

Analysis of resistance and risk factors of carbapenem-resistant *Klebsiella pneumoniae* to ceftazidime/avibactam

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Abstract: Objective To investigate the drug resistance and risk factors of ceftazidime/avibactam (CZA) use for carbapenem-resistant *Klebsiella pneumonia* (CRKP). **Methods** A total of 156 CRKP patients who were hospitalized in the ICU of Xi'an International Medical Center Hospital from October 2019 to May 2022 were selected and divided into CZA sensitive group (n=111) and resistant group (n=45) according to whether CRKP patients were resistant to CZA. The susceptibility of CRKP to CZA was detected by microbroth dilution method. The general data of CRKP-sensitive patients and CZA-resistant patients were analyzed and compared, and the risk factors of CRKP-resistant to CZA were analyzed by multivariate logistic regression. Mortality during hospitalization was compared between the two groups. **Results** Among the 156 CRKP isolates, 111 isolates (71.15%) were sensitive to CZA, and 45 isolates (28.85%) were resistant to CZA. There were no significant differences in age, gender, body mass index, specimen source and underlying diseases between the two groups (P>0.05). In invasive procedures, the proportion of patients undergoing mechanical ventilation (77.78% *vs.* 55.86%), dialysis (46.67% *vs.*18.02%) and surgery (77.78% *vs.* 54.05%) in the CZA-resistant group was significantly higher than that in the CZA-sensitive group (P<0.05). The proportion of patients who received CZA treatment in the CZA-resistant group was significantly higher than that in the CZA-sensitive group (24.44% *vs.* 9.01%), and the difference was statistically significant (P<0.05). Multivariate Logistic regression analysis showed that the risk factors of CRKP resistance to CZA included dialysis, mechanical ventilation and previous CZA treatment (P<0.05). The mortality rate during hospitalization in the CZA-resistant group (28.89%) was significantly higher than that in the CZA-sensitive group (10.81%), and the difference was statistically significant (χ^2=7.776, P =0.005). **Conclusions** Some CRKPs are resistant to CZA, and the mortality of drug-resistant patients is high during hospitalization. Dialysis, mechanical ventilation, and previous CZA treatment are risk factors for CZA resistance in CRKP.

Key words: Klebsiella pneumoniae; Drug resistance, bacterial; Carbapenem-resistant Klebsiella pneumoniae; Ceftazidime; Avibactam; Risk factors

近年来,导致院内感染的病原菌中肺炎克雷伯菌已成为我国仅次于大肠埃希菌的第二大革兰阴性病原菌[1]。碳青霉烯类是治疗多重耐药革兰阴性菌感染的重要抗菌药物。由于碳青霉烯类抗菌药物的广泛滥用,耐碳青霉烯肺炎克雷伯菌(carbapenem-resistant klebsiella pneumoniae,CRKP)的发病率越来越高[2]。产碳青霉烯类酶是导致CRKP耐药的重要机制,CRKP难以治疗,对人类健康构成了巨大威胁[3]。目前用于治疗耐碳青霉烯类肠杆菌感染的抗菌药物选择有限,包括多黏菌素、替加环素、磷霉素和氨基糖苷类[4]。头孢他啶-阿维巴坦(ceftazidime/avibactam,CZA)是FDA批准的第一个用于治疗碳青霉烯类耐药肠杆菌目所引起感染的新型β内酰胺合剂,可用于治疗成人复杂尿路感染、复杂腹腔感染、医院获得性肺炎和其他由需氧革兰阴性菌引起的感染[5]。CZA在控制CRKP感染方面疗效显著,是治疗CRKP感染的重要选择药物[6]。然而,在临床中,部分CRKP感染病人依旧存在对CZA耐药情况。因此,本研究分析比较了2019年10月至2022年5月在西安国际医学中心医院重症监护病房(intensive care unit,ICU)住院治疗的CRKP病人156例,探索CRKP对CZA耐药的危险因素,以此为CRKP临床治疗提供参考意见。

1 资料与方法

1.1 一般资料 收集西安国际医学中心医院ICU 2019年10月至2022年5月送检标本培养出CRKP的病人临床资料。根据纳入和排除标准筛选后,156例病人被纳入该回顾性分析。根据CRKP病人是否对CZA耐药分为CZA敏感组(n=111)和耐药组(n=45)。病人或其近亲属知情同意,本研究经西安国际医学中心医院伦理委员会批准(批号NQ-202046)。

纳入标准:(1)CRKP培养阳性病人;(2)具有CZA的抗菌药物敏感性试验;(3)完整的临床数据。排除标准:(1)年龄<18岁;(2)送检标本中包含除CRKP的其他病原菌;(3)病人临床资料不完整。

1.2 CZA判定标准 根据美国临床实验室标准化协会(clinical and laboratory standards institute,CLSI)2021年版标准(CLSI M100-S27),厄他培南的抑菌圈直径≤18mm、亚胺培南和美罗培南的抑菌圈直径≤19mm判断为耐药。美罗培南、亚胺培南或厄他培南三者中,至少对其中之一耐药的菌株为CRKP。对CZA进行最小抑菌浓度(minimal inhibitory concentration,MIC)检测。

1.3 研究方法 统计156例CRKP感染病人对CZA的药敏情况,分析比较CRKP对CZA敏感病人和耐药病人在年龄、性别、身体质量指数、标本来源、基础疾病、侵入性操作和既往接受CZA治疗上的差异,将两组病人一般资料中具有差异的指标纳入多因素logistic回归分析。比较两组病人住院期间的死亡率。

1.4 统计学方法 所有统计分析均使用SPSS 25.0进行处理,连续变量均符合正态分布,以$\bar{x}\pm s$表示,采用两独立样本t检验;分类变量使用百分比表示,采用χ^2检验。多因素logistic回归分析CRKP对CZA耐药的危险因素。P<0.05为差异有统计学意义。

2 结果

2.1 CRKP对CZA的药敏情况 采用微量肉汤稀释法检测CRKP对CZA的药敏情况,CZA MIC为0.5/4、1/4、2/4、4/4、8/4、16/4、32/4、64/4和>64/4 mg/L时,对应的菌株数量分别是5、22、36、33、15、8、5、4和28(根据CLSI M100-S27标准:CZA MIC ≤ 8/4 mg/L为敏感,CZA MIC ≥ 16/4 mg/L为耐药)。结果显示在156株CRKP中111株(71.15%)对CZA敏感,45株(28.85%)对CZA耐药。

2.2 CRKP对CZA敏感和耐药的病人一般资料比较 根据CRKP对CZA敏感和耐药的情况,将病人分为CZA敏感组和CZA耐药组。两组病人在年龄、性别、身体质量指数、标本来源、基础疾病和既往使用抗菌药物上差异无统计学意义(P>0.05)。在侵入性操作中,CZA耐药组机械通气、透析和手术的病人比例明显高于CZA敏感组(P<0.05),中心静脉置管、鼻胃管和导尿的病人比例上差异无统计学意义(P>0.05)。同时,CZA耐药组既往接受CZA治疗的病人比例明显高于CZA敏感组,差异有统计学意义(P<0.05)。见表1。

2.3 CRKP对CZA耐药危险因素多因素logistic回归分析 运用向前条件法进行多因素二元logistic回归分析,机械通气、透析、手术和既往接受CZA治疗为自变量,以CZA耐药情况为因变量。结果提示CRKP对CZA耐药的危险因素包括透析、机械通气和既往接受CZA治疗(P<0.05),与病人是否进行手术无关(P>0.05)。见表2。

2.4 CRKP感染病人住院期间死亡率 在CZA敏感组中CRKP感染病人住院期间死亡率为10.81%(12/111),在CZA耐药组中CRKP感染病人住院期间死亡率为28.89%(13/45)。CZA耐药组中病人住院期间死亡率明显高于CZA敏感组,差异有统计学意义(χ^2=7.78,P=0.005)。

3 讨论

CZA是第三代头孢菌素头孢他啶与阿维巴坦组成的复方制剂,阿维巴坦是一种新型合成β-内酰

表1 CRKP对CZA敏感和CRKP耐药的感染病人一般资料比较

一般资料	CZA敏感组(n=111)	CZA耐药组(n=45)	$\chi^2(t)$值	P值
人口统计学				
年龄/(岁,$\bar{x}$±s)	53.51±9.83	54.21±10.05	(0.40)	0.689
性别(男/女)/例	72/39	33/12	1.04	0.307
身体质量指数/(kg/m^2,$\bar{x}\pm s$)	23.54±3.04	24.02±2.86	(0.91)	0.365
标本来源/例(%)				
痰标本	47(42.34)	19(42.22)	0.00	0.989
血液标本	10(9.01)	4(8.89)	0.00	0.981
尿液标本	29(26.13)	9(20.00)	0.65	0.419
其他标本	25(22.52)	13(28.89)	0.70	0.401
基础疾病/例(%)				
呼吸系统	35(31.53)	13(28.89)	0.10	0.746
消化系统	16(14.41)	7(15.56)	0.03	0.856
泌尿系统	11(9.91)	5(11.11)	0.05	0.823
心血管系统	13(11.71)	6(13.33)	0.08	0.779
神经系统	26(23.42)	10(22.22)	0.03	0.872
其他系统	10(9.01)	4(8.89)	0.00	0.981
侵入性操作/例(%)				
中心静脉置管	102(91.89)	38(84.44)	1.93	0.165
鼻胃管	105(94.59)	39(86.67)	2.83	0.092
机械通气	62(55.86)	35(77.78)	6.54	0.011
透析	20(18.02)	21(46.67)	13.56	<0.001
导尿	105(94.59)	39(86.67)	2.83	0.092
手术	60(54.05)	35(77.78)	7.57	0.006
既往使用抗菌药物(≥7 d)/例(%)				
碳青霉烯类	104(93.69)	40(88.89)	1.04	0.308
氟喹诺酮类	37(33.33)	14(31.11)	0.07	0.789
替加环素	43(38.74)	17(37.78)	0.01	0.911
接受过CZA治疗/例(%)	10(9.01)	11(24.44)	6.55	0.011

注:CRKP为耐碳青霉烯类肺炎克雷伯菌,CZA为头孢他啶-阿维巴坦。

表2 CRKP对CZA耐药危险因素多因素logistic回归分析

危险因素	β值	$Wald\ \chi^2$值	P值	OR	95%CI
常数项	-9.24	5.88	0.015	0.00	
机械通气	1.85	5.62	0.018	3.10	(2.04,6.13)
透析	2.15	9.54	0.002	4.54	(2.55,9.35)
手术	1.02	3.56	0.059	1.25	(0.95,3.02)
既往接受CZA治疗	1.54	4.28	0.039	2.48	(1.42,3.62)

注:因变量为CZA耐药(赋值,耐药=1,敏感=0);自变量为机械通气、透析、手术和既往接受CZA治疗(赋值,有=1,无=0)。

胺酶抑制剂,能够抑制KPC(Amber A)和OXA-48(Amber D)类碳青霉烯酶。随着CZA的使用,CRKP对CZA的耐药性也在增加,研究显示2017年我国CRKP对CAZ的耐药率为34.3%[7],2018年为35.7%[8]。CRKP感染病人主要来源于ICU,同时ICU中CRKP感染病人死亡率高[9]。因此,在本研究中主要纳入我院ICU住院治疗的CRKP病人进行分析。

在本研究中,156株CRKP中111株(71.15%)对CZA敏感,45株(28.85%)对CZA耐药。在不同研究中,由于标本的来源不同,CRKP对CZA耐药率尚存在一定差异[10-11]。本研究中选取的CRKP感染病人均来自于ICU,由于ICU病人侵入性操作较多,住院时间长,病情重,因此ICU病人CRKP耐药的发生率较高。

产金属酶是对CZA耐药的重要机制之一,CZA耐药病人的死亡率明显升高。在本研究中根据CRKP对CZA敏感和耐药的情况,将病人分为CZA敏感组和CZA耐药组。两组病人在年龄、性别、身体质量指数、标本来源和基础疾病上差异无统计学意义。在侵入性操作中,CZA耐药组机械通气、透析和手术的病人比例明显高于CZA敏感组。同时,CZA耐药组既往接受CZA治疗的病人比例明显高于CZA敏感组。目前,有研究报道了住院病人中CRKP感染的危险因素,包括较长的住院和ICU停留时间、先前使用中心静脉导管、连续肾脏替代治疗、先前使用碳青霉烯类或氟喹诺酮类药物治疗[12-14]。在本研究结果和既往研究存在部分相同的危险因素,特别是病人接受侵入性操作后需要在临床中重点关注。

本研究中,多因素logistic回归分析显示CRKP对CZA耐药的危险因素包括透析、机械通气和既往接受CZA治疗。研究显示肾脏替代治疗是碳青霉烯类耐药肠杆菌科细菌感染病人CZA耐药性发展的独立预测因子[15]。肾脏替代疗法可能会为CRKP菌株的定植创造机会,并导致药物暴露不足,这可能导致CRKP对CZA耐药。机械通气的病人会使得痰液中培养出CRKP的比例增高,研究显示机械通气CRKP感染病人对CZA耐药的比例明显增加[16]。在既往接受过CZA治疗,特别是在不规范的治疗中,更容易导致CRKP对CZA耐药[17]。

对于CRKP耐药病人,CZA耐药组中病人住院期间死亡率(28.89%)明显高于CZA敏感组(10.81%)。CRKP死亡率的风险因素可能因研究人群、地区和感染类型而异。研究显示既往住院、长期住院、使用β-内酰胺酶抑制剂、肌酐水平较高、与其他耐药菌合并感染是CRKP感染死亡的独立危险因素[18-19]。在本研究中CZA耐药组CRKP病人的死亡率明显增加,这也提示在治疗过程中需关注CZA耐药情况。

综上所述,在ICU中依旧存在较高的CRKP感染病人对CZA耐药,耐药病人住院期间死亡率高。

透析、机械通气和既往接受CZA治疗是CRKP对CZA耐药的危险因素。在临床治疗中,需要重点关注这些危险因素。

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