

· 临床研究 · doi:10.3969/j.issn.1671-8348.2024.02.008

网络首发 [https://link.cnki.net/urlid/50.1097.R.20231012.1416.010\(2023-10-12\)](https://link.cnki.net/urlid/50.1097.R.20231012.1416.010(2023-10-12))

儿童 CRKP 感染的临床特征及预后不良危险因素研究*

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[摘要] **目的** 分析儿童耐碳青霉烯类肺炎克雷伯菌(CRKP)感染的临床特征、耐药性及预后不良危险因素。**方法** 收集 2016 年 8 月 5 日至 2020 年 12 月 31 日该院分离的住院患儿分离 CRKP 标本,对 CRKP 阳性患儿临床资料和 CRKP 耐药性进行分析,对 CRKP 感染患儿预后良好组和预后不良组的相关资料进行比较,并分析预后不良的危险因素。**结果** 共收集 106 株非重复 CRKP,主要分离自≤1 岁患儿。科室分布以新生儿重症医学科和重症医学科为主。CRKP 对多种抗菌药物呈高耐药,仅对阿米卡星、左氧氟沙星、庆大霉素、环丙沙星、米诺环素、氯霉素的耐药率<30%。CRKP 感染患儿预后不良率达 27.4%。logistic 多因素回归分析结果显示,多器官功能障碍和贫血是 CRKP 感染患儿预后不良的独立危险因素($P<0.05$)。**结论** 儿童 CRKP 感染以≤1 岁婴儿为主,CRKP 对多种抗菌药物呈高度耐药,预后不良的独立危险因素包括多器官功能障碍和贫血。

[关键词] 耐碳青霉烯类肺炎克雷伯菌;耐药性;危险因素;多器官功能障碍;贫血

[中图法分类号] R978 **[文献标识码]** A **[文章编号]** 1671-8348(2024)02-0198-06

Clinical characteristics of children patients with carbapenem resistant *Klebsiella pneumoniae* infection and risk factors for poor prognosis*

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[Abstract] **Objective** To analyze the clinical characteristics, drug resistance and risk factors for poor prognosis in children patients with carbapenem resistant *Klebsiella pneumoniae* (CRKP) infection. **Methods** The samples of CRKP isolated from the children inpatients in this hospital from August 5, 2016 to December 31, 2020 were collected. The clinical data and drug resistance of CRKP in the patients with CRKP positive were analyzed. The risk factors in the poor prognosis group and good prognosis group of children patients with CRKP infection conducted the correlation analysis. **Results** A total of 106 strains of non-repetitive CRKP were collected, which were mainly isolated from the patients ≤ 1 year old. The department distribution was dominated by the neonatal ICU and comprehensive ICU. CRKP showed the high resistance to multiple antibacterial drugs, and its resistance rates to amikacin, levofloxacin, gentamicin, ciprofloxacin, minocycline and chloramphenicol were less than 30%. The poor prognosis rate in the children patients with CRKP infection reached 27.4%. The logistic multivariate regression analysis results showed that the multiple organ dysfunction and anemia were the independent risk factors for poor prognosis in the children patients with CRKP infection ($P<0.05$). **Conclusion** The children CRKP infection is mainly the infants ≤ 1 years old, and CRKP shows the high resistance to multiple antibacterial drugs, the independent risk factors of poor prognosis include the multiple organ dysfunction and anemia

[Key words] carbapenem resistant *Klebsiella pneumoniae*; drug resistance; risk factors; multiple organ dysfunction; anemia

* 基金项目:广西壮族自治区卫生健康委员会自筹经费科研课题(Z-A20220257);广西壮族自治区临床重点专科建设项目(桂卫医发〔2020〕15号)。[△] 通信作者, E-mail: 16485383@qq.com.

肺炎克雷伯菌(*Klebsiella pneumoniae*, KP)是院内感染常见的革兰阴性致病菌。近年来,因抗菌药物的过度使用、实验室检测能力的提升等原因,碳青霉烯类耐药肺炎克雷伯菌(carbapenem resistant *Klebsiella pneumoniae*, CRKP)的检出率明显上升^[1-4]。由于 CRKP 毒力强、对多种抗菌药物产生耐药,感染 CRKP 的患者病情往往进展迅速,患者治疗失败率增加,致死率高达 20%~70%^[5-9]。目前,关于儿童感染 CRKP 的报道相对较少,为了解儿童 CRKP 感染的临床特点、患儿的预后转归及不良预后相关危险因素,作者对本院 106 例 CRKP 感染患儿进行回顾性分析,以为临床诊疗和院内感染防控提供参考,现报道如下。

1 资料与方法

1.1 一般资料

收集 2016 年 8 月 5 日至 2020 年 12 月 31 日本院 KP 感染病例 873 例,其中 CRKP 感染病例 106 例。纳入标准:(1)年龄<18 岁;(2)病历资料完整;(3)符合 CRKP 感染诊断标准。同一患儿仅留取 1 株标本。

1.2 方法

标本采集及培养严格按照《全国临床检验操作规程》操作,血培养采用 BacT/Alert3D 全自动血培养仪(法国生物梅里埃公司);菌种鉴定及药敏试验采用 DL-96 II 细菌测定药敏系统(珠海迪尔生物工程有限公司)和 VITEK 2-Compact 全自动细菌分析仪(法国生物梅里埃公司)及相应卡片。厄他培南、亚胺培南和美罗培南药敏结果进一步采用纸片法确认,结果判读参照美国临床实验室标准委员会(clinical and laboratory standard institute, CLSI) 2020 年判断标准进行。

1.3 统计学处理

采用 SPSS26.0 软件进行数据分析。计量资料以 $M(Q_1, Q_3)$ 表示,组间比较采用秩和检验;计数资料以例数或百分比表示,组间比较采用 χ^2 检验。将单因素分析中差异有统计学意义的因素纳入 logistic 回归模型进行多因素分析。以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 CRKP 及病原菌检出情况

在检出的 873 株 KP 中,CRKP 106 株,耐药率为 12.1%。2016 年检出 CRKP 24 株,即年耐药率为 22.6%(24/106);2017 年检出 40 株,即年耐药率为 20.4%(40/196);2018 年检出 18 株,即年耐药率为 10.2%(18/176);2019 年检出 7 株,即年耐药率为 4.2%(7/167);2020 年检出 17 株,即年耐药率为 7.5%(17/228)。

2.2 CRKP 感染临床特征

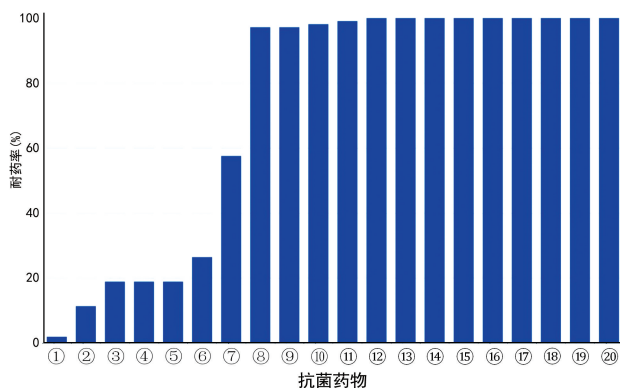
CRKP 感染患儿中,以年龄 ≤ 1 岁的婴儿为主,其中新生儿(1~28 d)41 例(38.7%); > 28 d 至 1 岁的婴儿 53 例(50.0%)。CRKP 感染患儿中,男 65 例(61.3%),早产儿 67 例(63.2%)。标本主要为痰液(47.2%)、血(19.8%)和肺泡灌洗液(15.1%)。科室分布主要是新生儿重症医学科(51.9%),其次为重症医学科(28.3%),见表 1。

表 1 CRKP 感染患儿临床特征($n=106$)

项目	例数(n)	构成比(%)
年龄		
1~28 d	41	38.7
>28 d 至 1 岁	53	50.0
>1~3 岁	8	7.5
>3~6 岁	2	1.9
>6~12 岁	2	1.9
孕周		
早产儿	67	63.2
非早产儿	39	36.8
性别		
男	65	61.3
女	41	38.7
标本类型		
痰液	50	47.2
血	21	19.8
肺泡灌洗液	16	15.1
其他	19	17.9
科室分布		
新生儿重症医学科	55	51.9
重症医学科	30	28.3
儿外科	5	4.7
其他科室	16	15.1
治疗结局		
痊愈	50	47.2
病情好转	27	25.5
转院/主动出院	23	21.7
放弃治疗	2	1.9
死亡	4	3.8

2.3 CRKP 耐药分析

常用抗菌药物中,CRKP 对阿米卡星的耐药率最低(1.9%),其次为左氧氟沙星(11.3%),庆大霉素、环丙沙星和米诺环素耐药率均为 18.9%,氯霉素和复方磺胺甲噁唑的耐药率分别为 26.4%和 57.6%,其他抗菌药物耐药率均 $> 90\%$,见图 1。



①:阿米卡星;②:左氧氟沙星;③:庆大霉素;④:环丙沙星;⑤:米诺环素;⑥:氯霉素;⑦:复方磺胺甲噁唑;⑧:头孢哌酮/舒巴坦;⑨:亚胺培南;⑩:替卡西林/克拉维酸;⑪:哌拉西林/他唑巴坦;⑫:头孢唑林;⑬:头孢呋辛;⑭:头孢吡肟;⑮:氨苄西林;⑯:头孢西丁;⑰:头孢曲松;⑱:氨苄西林/舒巴坦;⑲:美罗培南;⑳:头孢他啶。

图 1 CRKP 对抗菌药物的耐药率

2.4 治疗结局

106 例 CRKP 感染患儿中,50 例(47.2%)痊愈;

27 例(25.5%)病情好转;23 例(21.7%)治疗效果不佳,进行转院治疗;2 例(1.9%)放弃治疗;4 例(3.8%)死亡。4 例死亡患儿均为早产低体重儿,均有先天性心脏病和凝血功能障碍,其中 3 例出现多脏器功能损伤。其中,痊愈和病情好转的患儿纳入预后良好组(77 例,占 72.6%);其他患儿纳入预后不良组(29 例,占 27.4%)。

2.5 预后良好组和预后不良组相关资料比较

两组患儿神经脑部基础疾病、多器官功能障碍和贫血构成比差异有统计学意义($P < 0.05$),见表 2。

2.6 预后影响因素 logistic 回归分析

以两组相关资料比较中差异有统计学意义的变量为自变量,以是否预后不良为因变量,二分类 logistic 回归分析结果显示:多器官功能障碍($OR = 5.571$, $95\%CI: 1.429 \sim 21.709$)和贫血($OR = 3.363$, $95\%CI: 1.024 \sim 11.044$)是患儿感染 CRKP 治疗效果不良的独立危险因素,见表 3。

表 2 预后良好组和预后不良组相关资料比较

项目	预后良好组($n=77$)	预后不良组($n=29$)	P
住院总时间[$M(Q_1, Q_3)$, d]	11.00(7.00, 14.00)	27.00(17.00, 44.00)	0.644
C 反应蛋白[$M(Q_1, Q_3)$, mg/L]	5.60(1.92, 37.42)	8.85(1.96, 16.76)	0.654
降钙素原[$M(Q_1, Q_3)$, ng/L]	0.61(0.11, 1.98)	0.21(0.14, 3.70)	0.250
PLT[$M(Q_1, Q_3)$, $\times 10^9/L$]	326.00(142.00, 478.00)	270.00(137.00, 387.00)	0.229
WBC[$M(Q_1, Q_3)$, $\times 10^9/L$]	11.70(8.20, 15.70)	7.8(6.00, 12.40)	0.085
中性粒细胞数[$M(Q_1, Q_3)$, $\times 10^9/L$]	6.14(3.48, 8.25)	3.85(2.61, 10.32)	0.367
淋巴细胞数[$M(Q_1, Q_3)$, $\times 10^9/L$]	3.21(1.85, 4.34)	2.43(1.33, 3.46)	0.182
性别[$n(\%)$]			0.980
男	48(62.3)	18(62.1)	
女	29(37.7)	11(37.9)	
黄疸[$n(\%)$]			0.984
有	40(51.9)	15(51.7)	
无	37(48.1)	14(48.3)	
心血管系统基础疾病[$n(\%)$]			0.162
有	21(27.3)	12(41.4)	
无	56(72.7)	17(58.6)	
消化系统基础疾病[$n(\%)$]			0.313
有	19(24.7)	10(34.5)	
无	58(75.3)	19(65.5)	
代谢电解质紊乱[$n(\%)$]			0.486
有	34(44.2)	15(51.7)	
无	43(55.8)	14(48.3)	
神经脑部基础疾病[$n(\%)$]			0.028
有	20(26.0)	14(48.3)	
无	57(74.0)	15(51.7)	
多器官功能障碍[$n(\%)$]			0.011

续表 2 预后良好组和预后不良组相关资料比较

项目	预后良好组($n=77$)	预后不良组($n=29$)	P
有	5(6.5)	7(24.1)	
无	72(93.5)	22(75.9)	
留置导管[$n(\%)$]			0.346
有	6(7.8)	4(13.8)	
无	71(92.2)	25(86.2)	
气管插管[$n(\%)$]			0.486
有	35(45.5)	11(37.9)	
无	42(54.5)	18(62.1)	
有创手术[$n(\%)$]			0.322
有	24(31.2)	12(41.4)	
无	53(68.8)	17(58.6)	
贫血[$n(\%)$]			0.005
有	47(61.0)	26(89.7)	
无	30(39.0)	3(10.3)	
休克史[$n(\%)$]			0.071
有	16(20.8)	11(37.9)	
无	61(79.2)	18(62.1)	
早产[$n(\%)$]			0.762
有	48(62.3)	19(65.5)	
无	29(37.7)	10(34.5)	
使用糖皮质激素[$n(\%)$]			0.745
有	24(31.2)	10(34.5)	
无	53(68.8)	19(65.5)	
使用抗真菌药物[$n(\%)$]			0.257
有	33(42.9)	16(55.2)	
无	44(57.1)	13(44.8)	
合并其他感染[$n(\%)$]			0.974
有	21(27.3)	8(27.6)	
无	56(72.7)	21(72.4)	

表 3 CRKP 感染患儿预后影响因素 logistic 回归分析

项目	B	SE	P	OR	95% CI
神经脑部基础疾病(有 vs. 无)	0.650	0.485	0.180	1.916	0.740~4.959
多器官功能障碍(有 vs. 无)	1.718	0.694	0.013	5.571	1.429~21.709
贫血(有 vs. 无)	1.213	0.607	0.046	3.363	1.024~11.044

3 讨 论

CRKP 是指对亚胺培南、美罗培南及厄他培南中任一种碳青霉烯类抗菌药物耐药的 KP。本研究 873 例 KP 感染患儿中,CRKP 感染患儿 106 例,对碳青霉烯类药物的耐药率为 12.1%。根据中国细菌耐药监测网(<http://www.chinets.com/>)报道,我国 CRKP 的整体耐药率呈上升趋势,2005 年 KP 对美罗培南的耐药率为 2.9%,2019 年耐药率则达到 26.8%^[6]。

CRKP 感染人群中,以 ≤ 1 岁的婴儿为主,其中新生儿(1~28 d)占 38.7%, >28 d 至 1 岁的婴儿占 50.0%,患儿以男性、早产儿较为常见。儿童 CRKP 感染分布于医院各科室,主要是新生儿重症医学科,其次为重症医学科,原因主要为上述科室患儿病情危重,免疫力低下,住院时间相对较长,多伴有严重的基础疾病,需接受多种抗菌药物治疗,接受多种侵袭性诊疗操作。

KP 对碳青霉烯类药物的耐药机制主要包括产碳青霉烯酶、青霉素结合蛋白靶位结构发生改变、产高水平头孢菌素酶或超广谱 β 内酰胺酶合并外膜孔蛋白突变等^[10-12]。产碳青霉烯酶是细菌对碳青霉烯类药物耐药最主要的分子机制^[1,13-16]。本研究结果显示,CRKP 对多种抗菌药物高度耐药,仅对阿米卡星、左氧氟沙星、庆大霉素、环丙沙星、米诺环素、氯霉素的耐药率低于 30%;CRKP 对复方磺胺甲噁唑的耐药率为 57.6%,对其他抗菌药物耐药率皆 >90%,提示 CRKP 菌株对青霉素类及头孢菌素类抗菌药物耐药率过高,阿米卡星耐药率较低可能是因为阿米卡星不被碳青霉烯酶和超广谱 β 内酰胺酶分解,且对多种氨基糖苷类钝化酶稳定。

CRKP 是临床上较为常见的耐药菌之一,具有毒力强、高耐药、高致死率等特点,患者预后往往不理想^[7,17-20]。本研究 106 例 CRKP 感染患儿中,预后不良者(转院、放弃治疗、死亡)29 例,占总例数的 27.4%。研究 CRKP 感染患儿预后不良的危险因素对于提高 CRKP 感染诊疗能力、改善 CRKP 感染患儿预后、降低 CRKP 感染致死率具有重要意义。以往研究发现,基础疾病、入院前碳青霉烯类治疗、初始治疗后格拉斯哥昏迷指数、住院期间并发症、初始治疗后急性生理学和慢性疾病分类系统 II 评分等是 CRKP 感染预后不良的危险因素^[21-26]。本研究结果显示,两组间神经脑部基础疾病、多器官功能障碍和贫血构成比差异有统计学意义($P < 0.05$)。多因素 logistic 回归分析结果显示,多器官功能障碍和贫血是 CRKP 感染患儿预后不良的独立危险因素。多器官功能障碍涉及多个脏器受损,患者出现损伤的脏器越多,其预后一般越差。婴儿严重感染合并贫血易出现缺氧、高碳酸血症、癫痫发作、脑出血等症状,一旦出现脑室出血,其认知和运动神经严重受损,致死率较高。

综上所述,本研究对 CRKP 感染患儿的临床特征、耐药性及治疗预后进行回顾性分析,对 CRKP 感染治疗效果不良的危险因素进行统计,发现多器官功能障碍和贫血是 CRKP 感染患儿预后不良的独立危险因素。

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