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ICU 肾功能不全患者耐碳青霉烯类肺炎克雷伯菌的分布特征及耐药特性分析*

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摘要 目的:调查与分析重症监护病房(ICU, Intensive Care Unit)肾功能不全患者耐碳青霉烯类肺炎克雷伯菌的分布特征及耐药特性。**方法:**收集 2015 年 2 月到 2017 年 12 月入住我院 ICU 的合并肾功能不全的感染性患者标本 46 例,调查标本来源与患者的临床资料,分离鉴定病原菌并进行耐药特性分析。**结果:**46 例患者中共分离出 165 株耐碳青霉烯类肺炎克雷伯菌,标本来源于尿液 6 例,痰液 20 例,血液 4 例,肺泡灌洗液 10 例,分泌物 3 例,胆汁 3 例。165 株耐碳青霉烯类肺炎克雷伯菌对美罗培南、亚胺培南、厄他培南、头孢噻吩、头孢噻肟、氨苄西林、阿莫西林/克拉维酸、环丙沙星的耐药率在 80%以上,对哌拉西林/他唑巴坦、庆大霉素的耐药率在 75%左右,对米诺环素、四环素、替加环素的耐药率均在 40%以下。46 例患者中,治愈 16 例,好转 17 例,无效 13 例,总有效率为 71.74%;ICU 平均住院天数为(11.48±2.11)d;总住院天数为(45.29±1.48)d,院内病死 11 例,病死率为 23.91%。多因素 Logistic 回归分析结果显示深静脉置管置入(OR=1.893)、年龄≥65 岁(OR=2.154)、使用碳青霉烯类抗菌药物(OR=2.041)为 ICU 肾功能不全患者发生耐碳青霉烯类肺炎克雷伯菌感染的独立危险因素($P<0.05$)。**结论:**ICU 肾功能不全患者耐碳青霉烯类肺炎克雷伯菌多来源于痰液标本,对米诺环素、四环素、替加环素的耐药性低,在临床上可以选择此类药物,合理把握用药的时间和剂量,增强抗感染的效率。同时,深静脉置管置入、年龄≥65 岁、使用碳青霉烯类抗菌药物为治疗过程中主要的危险因素,在 ICU 肾功能不全患者治疗中,应该重点考虑,提高治疗效率。

关键词:重症监护病房;肾功能不全;耐碳青霉烯类肺炎克雷伯菌;耐药性

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Distribution and Drug Resistance Characteristics of Carbapenem Resistant *Klebsiella Pneumoniae* in Patients with Renal Insufficiency in ICU*

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ABSTRACT Objective: To investigate and analyze the distribution and drug resistance of carbapenem-resistant *Klebsiella pneumoniae* in patients with renal insufficiency in intensive care unit (ICU). **Methods:** From February 2015 to December 2017, 46 specimens of patients with renal insufficiency in ICU were collected. The source of specimen and the clinical data of patients were investigated, the pathogens were isolated and identified. **Results:** A total of 165 strains of Carbapenem resistant *Klebsiella pneumoniae* were isolated from 46 cases of patients. The specimens were derived from 6 cases of urine, 20 cases of sputum, 4 cases of blood, 10 cases of lavage fluid, 3 cases of secretion, 3 cases of bile. The resistance rates of 165 strains of carbapenem-resistant *Klebsiella pneumoniae* to meropenem, imipenem and ertapenem, retinoic acid and ciprofloxacin, cefalotin, cefotaxime, ampicillin, amoxicillin/carat were over 80%, and the resistance rates to piperacillin/tazobactam and gentamicin were about 75%, and for the tetracycline and tega were below 40%. Among the 46 patients, there were 16 cases were cured, 17 cases were improved, 13 cases were ineffective, and the total effective rates were 71.74%; the average hospital stay in ICU were (11.48±2.11)d; the total hospital stay were (45.29±1.48)d, and the hospital died were 11 case that the rates 23.91%. Multivariate logistic regression analysis showed deep venous catheterization (OR=1.893), age≥65 years (OR=2.154), use of carbapenem antibiotics (OR=2.041) for ICU patients with renal insufficiency Patients had independent risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection ($P<0.05$). **Conclusion:** The patients with renal insufficiency in ICU are resistant to carbapenem-resistant *Klebsiella pneumoniae*, which are mostly derived from sputum specimens and have low resistance to minocycline, tetracycline and tigecycline. These drugs can be selected clinically. Reasonably grasp the time and dosage of medication, and enhance the efficiency of anti-infection. At the same time, deep venous catheter placement, age ≥ 65 years, the use of carbapenem antibiotics as the main risk factors in the treatment process, in the treatment of ICU patients with renal insufficiency, should be

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considered, improve treatment efficiency.

Key words: Intensive care unit; Renal insufficiency; Carbapenem resistant *Klebsiella pneumoniae*; Drug resistance

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前言

重症监护病房(Intensive Care Unit, ICU)多收治临床上的危重疾病,肾功能不全患者进入 ICU 多表现为肾功能衰竭、免疫功能低下,容易并发各种院内感染^[1,2]。相关研究显示 ICU 肾功能不全患者的院内感染发生率接近 4%,特别是很多患者在诊治中需要进行侵入性操作,抗菌药物、免疫抑制剂、激素的应用也比较多,增加了发生院内感染的风险^[3,4]。

肺炎克雷伯菌是临床上常见的条件致病菌之一,是临床上常见的泛耐药菌之一,极易产生耐药性^[5]。该菌可产生质粒介导的超广谱 β 内酰胺酶(ESBLs)和头孢菌素酶(AmpC),从而对三代头孢菌素、氨基糖苷有很好的耐药性^[6,7]。当前研究显示肺炎克雷伯菌可产生对碳青霉烯类抗菌药物耐药的碳青霉烯酶^[8,9]。随着近年来耐碳青霉烯类药物广泛的使用,耐碳青霉烯类肺炎克雷伯菌当前在我国的发病感染病例有逐年上升趋势,且院内有爆发性传播的特点,可使得患者陷入难以诊治的困境,严重威胁患者的预后^[10-13]。本研究主要回顾性分析了 ICU 肾功能不全患者耐碳青霉烯类肺炎克雷伯菌 165 株,探讨了其分布特征,并进行了耐药性分析,以期临床合理选择治疗药物与改善患者预后提供参考,现将结果总结报道如下。

1 资料与方法

1.1 一般资料

采用回顾性、总结性研究方法收集 2015 年 2 月到 2017 年 12 月我院 ICU 收治的肾功能不全患者标本 46 例,纳入标准:临床、检验学资料完整;对于同一患者的多部位感染,则以第一个培养阳性菌株列入研究;患者所携带的病原菌经细菌培养鉴定为肺炎克雷伯菌,全部病例均符合中华医学会制定的《医院感染诊断标准》;耐药性检测判断为耐碳青霉烯类肺炎克雷伯菌;临床表现为寒战、发热、外周血白细胞和中性粒细胞的显著增多或减少。排除标准:入院时就存在肺炎克雷伯菌感染的患者;相临床、检验学不完整者;碳青霉烯类抗菌药物过敏试验表现为中介;重复标本患者;未经抗菌药物治疗或治疗时间少于 24h 的患者;病原学培养阳性但不伴临床症状的患者。本研究所有患者均签署知情同意书,并得到了医院伦理委员会的批准。

1.2 细菌鉴定

46 例患者的标本类型包括尿液、痰液、血液、肺泡灌洗液、分泌物、胆汁等。标本 2 h 内送检,根据标本类型进行相应平板接种,并置于 37℃ 温箱孵育,应用全自动细菌分析仪(法国生物梅里埃 VITEK2 GN Test Kit)进行细菌鉴定,质控菌株为肺炎克雷伯菌 ATCC700603。

1.3 药敏及耐药分析

分离待测微生物后,应用革兰阴性细菌药敏卡片(VITEK 2 AST-XN04 Test Kit 及 VITEK 2 AST-GN67 Test Kit)进行药

敏测定。

1.4 临床资料调查

调查与记录所有患者的临床资料,包括性别、年龄、合并疾病、深静脉置管置入、体重指数、初始诊断、使用碳青霉烯类抗菌药物、总住院天数、ICU 住院天数、预后等。

疗效标准:感染临床症状和体征全部消失,痊愈出院判定为治愈;感染临床症状和体征部分消失,或由 ICU 转入普通病房继续治疗判定为好转;未见好转甚至出现恶化甚至死亡判定为无效。

1.5 统计学分析

选择 SPSS20.00 软件进行分析,计量数据、计数数据分别采用均数 $\pm$ 标准差、百分比表示,组间分别采用 t 检验、卡方检验等,多因素分析采用多因素 Logistic 回归分析,以 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 患者的一般临床资料

46 例患者中,共分离出 165 株耐碳青霉烯类肺炎克雷伯菌,包括男 26 例,女 20 例;年龄最小 27 岁,最大 93 岁,平均年龄(56.39 ± 2.82)岁;平均体重指数(20.58 ± 2.91)kg/m²;合并疾病:糖尿病 13 例,高血压 9 例,冠心病 6 例,呼吸道感染疾病 5 例;原发疾病:糖尿病肾病 10 例,高血压肾病 5 例,尿毒症 22 例,肾功能衰竭 9 例。

2.2 标本来源

在 46 例患者中,标本来源于尿液 6 例,痰液 20 例,血液 4 例,肺泡灌洗液 10 例,分泌物 3 例,胆汁 3 例,构成比分别为 13.04%、43.48%、8.70%、21.74%、6.52%和 6.52%。

2.3 耐药特性

165 株耐碳青霉烯类肺炎克雷伯菌对美罗培南、亚胺培南、厄他培南、头孢噻吩、头孢噻肟、氨苄西林、阿莫西林/克拉维酸、环丙沙星、庆大霉素的耐药率在 80%以上;耐药率在 75%左右的药物包括:哌拉西林/他唑巴坦;耐药率均在 40%以下的药物包括:米诺环素、四环素、替加环素。见表 1。

2.4 预后情况

46 例患者中,治愈 16 例,好转 17 例,无效 13 例,总有效率为 71.74%。ICU 平均住院天数为(11.48 ± 2.11)d;总住院天数为(45.29 ± 1.48)d,院内病死 11 例,病死率为 23.91%。

2.5 ICU 肾功能不全患者患者发生耐碳青霉烯类肺炎克雷伯菌感染的影响因素

以耐碳青霉烯类肺炎克雷伯菌感染作为因变量,以 ICU 肾功能不全患者临床资料作为自变量,多因素 Logistic 回归分析结果显示深静脉置管置入($OR=1.893$)、年龄 ≥ 65 岁($OR=2.154$)、使用碳青霉烯类抗菌药物($OR=2.041$)为 ICU 肾功能不全患者患者发生耐碳青霉烯类肺炎克雷伯菌感染的独立危险因素($P < 0.05$),见表 2。

表 1 ICU 肾功不全患者耐碳青霉烯类肺炎克雷伯菌的耐药特性(n=165)

Table 1 Drug resistance characteristics of carbapenem resistant *Klebsiella pneumoniae* in patients with ICU renal insufficiency (n=165)

Index	Strain	Drug-resistant strain	Drug resistance rate(%)
Meropenem	165	136	82.42
Imipenem	165	137	83.03
Ertapenem	165	140	84.85
Cephalothin	165	138	83.64
Cefotaxime	165	137	83.03
Ampicillin	165	139	84.24
Amoxicillin / clavulanic acid	165	139	84.24
Ciprofloxacin	165	138	83.64
Piperacillin/Tazobactam	165	122	73.94
Gentamycin	165	128	77.58
Minocycline	165	56	33.94
Tetracycline	165	34	20.61
Tigecycline	165	22	13.33

表 2 ICU 肾功不全患者耐碳青霉烯类肺炎克雷伯菌发生的多因素分析(n=46)

Table 2 Multivariate analysis of the incidence of carbapenem resistant *Klebsiella pneumoniae* in patients with ICU renal insufficiency (n=46)

Variable	β	SE	Wald	P	OR(95%CI)
Deep vein catheterization	0.323	0.178	34.119	0.000	1.893(1.541-2.386)
Age $\geq$ 65 years	0.627	0.208	34.396	0.000	2.154(1.82-2.737)
Use of carbapenem antibiotics	0.451	0.196	28.175	0.000	2.041(1.885-2.786)

3 讨论

ICU 肾功不全患者合并院内感染当前在临床上比较常见,肺炎克雷伯菌是当前常见的革兰阴性菌,是我国院内感染的第二大致病菌^[14,15]。肺炎克雷伯菌极易感染机体免疫低下的老年患者、肾功能衰竭等患者,在老年病房、ICU 病房等病区通常具有较高的肺炎克雷伯菌检出率^[16-18]。肺炎克雷伯菌感染可引起肺炎、败血症、脑膜炎、尿路感染,严重情况下导致患者死亡。随着 β -内酰胺酶类、碳青霉烯类等抗菌药物的广泛使用,肺炎克雷伯菌的耐药性不断升高^[19,20]。碳青霉烯类抗菌药物是临床治疗肺炎克雷伯菌感染最有效的抗菌药物,但当前该菌对碳青霉烯类抗菌药物的耐药率也在一直升高。本研究显示 46 例肾功能不全患者的尿液、痰液、血液等中共分离出 165 株耐碳青霉烯类肺炎克雷伯菌。有学者也从临床上分离了 173 株肺炎克雷伯菌,主要分布在肺部感染、血液感染。当前,也有研究显示肺炎克雷伯菌在痰液中分布最广,其次为血液^[21,22]。

肺炎克雷伯菌属是 ICU 院内感染的重要致病菌,在抗感染过程中,抗菌药物的使用 and 选择很重要。当前肺炎克雷伯菌的耐药性日趋严重,给临床诊治带来极大的困难,同时加重了抗菌药物的量和频率,促进了耐药菌大量繁殖。抗菌药物的选择作用造成耐药基因在同种或不同菌种转移^[23]。因此,肺炎克

雷伯菌的耐药性不断增加,控制越来越难。有研究显示肺部感染中的耐碳青霉烯类的肺炎克雷伯菌对氨苄西林、哌拉西林舒巴坦钠、氨苄西林、头孢曲松、头孢噻林的耐药率均为 95.0%以上^[24,25]。本研究结果也显示耐碳青霉烯类肺炎克雷伯菌对美罗培南、亚胺培南、厄他培南、头孢噻吩、头孢噻肟、氨苄西林、阿莫西林/克拉维酸、环丙沙星、庆大霉素的耐药率达到了 80%以上,对米诺环素、四环素、替加环素的耐药率均在 40%以下。以上结果提示在选择抗感染的药物治疗肺炎克雷伯菌时,可以选择耐药性低的药,如米诺环素、四环素、替加环素,增加抗感染的效率。肺炎克雷伯菌的对碳青霉烯类抗菌药物的耐药机制有外排泵的过度表达、生物被膜的形成、产碳青霉烯酶、外膜蛋白的缺失与突变等^[26]。甘氨酸环类抗菌药物米诺环素、四环素、替加环素通过与细菌 30S 核糖体强有力的结合,从而阻止细菌蛋白质的合成,达到抗菌目的^[27]。特别是替加环素具有抗菌谱广、耐药率低、抗菌活力强的特点,当前在临床上的应用也比较多^[28]。

ICU 住院期间患者的治愈结果显示总有效率为 71.74%,住院的时间均在一个月以上,院内病死率为 23.91%。当前,也有研究显示耐碳青霉烯类肺炎克雷伯菌感染患者和非耐碳青霉烯类肺炎克雷伯菌感染患者之间的临床治疗效果、感染后住院天数、院内病死率均有显著差异,耐碳青霉烯类肺炎克雷伯

菌感染患者预后更差^[29],提示肺炎克雷伯菌感染直接关系到患者的存活率,合理用药治疗显得十分重要。耐碳青霉烯类肺炎克雷伯菌的耐药机制复杂,产碳青霉烯酶是其中最主要的机制之一,该酶能够水解头孢菌素类、青霉素类、碳青霉烯类、类抗菌药物而使菌株产生耐药性,阻碍药物发挥抗炎的作用,影响治疗效果。多因素 Logistic 回归分析结果显示深静脉置管置入、年龄 ≥ 65 岁、使用碳青霉烯类抗菌药物为 ICU 肾功不全患者发生耐碳青霉烯类肺炎克雷伯菌感染的独立危险因素,其原因可能是深静脉置管置入可破坏机体本身的生理环境,使大量细菌上行至膀胱、输尿管、肾盂等引起感染,同时细菌在深静脉管表面寄生,形成细菌生物膜,影响机体的免疫能力,引起患者感染^[30]。部分患者随着年龄的增大,机体的各项生理机能也在不断下降,当深静脉置管置入时更容易增加疾病的易感性^[31]。当前抗菌药物的大量使用及不合理用药是细菌耐药性产生的主要因素。为此,医院需要加强医院感染控制管理,及时消毒,严格严防耐药菌的暴发流行,严格控制耐药菌的传播。本研究虽然在临床上对肾功不全患者耐碳青霉烯类肺炎克雷伯菌的选择用抗炎药有一定的指示作用,但在研究中也存在一些不足。首先,研究的样本数量不足,且对于危险因素的分析调查不够深入,耐药特性分析所选择的抗菌药物也有所遗漏,将在下一步进行深入分析。

总之,ICU 肾功不全患者耐碳青霉烯类肺炎克雷伯菌多来源于痰液标本,此类患者极易发生下呼吸道感染,对米诺环素、四环素、替加环素的耐药性低,在临床上可以选择此类药物,把握用药的时间和剂量,发挥抗感染的效率。同时,深静脉置管置入、年龄 ≥ 65 岁、使用碳青霉烯类抗菌药物为治疗过程中主要的危险因素,在 ICU 肾功不全患者治疗中,应该重点考虑,提高治疗效率。

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(上接第 1897 页)

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