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· 论 著 ·

血液肿瘤患者耐碳青霉烯类肺炎克雷伯菌医院获得性血流感染疑似暴发调查与控制

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[摘要] 目的 对一起耐碳青霉烯类肺炎克雷伯菌(CRKP)医院获得性血流感染疑似暴发事件进行追踪调查, 为有效控制 CRKP 感染提供依据。**方法** 于 2022 年 6 月在某教学医院成人血液科运用现场流行病学调查获取 CRKP 感染患者特征及造成事件传播的危险因素, 采用血营养琼脂培养基现场接种法对病区进行环境采样寻找目标菌(CRKP), 比较采取控制措施后环境微生物清除状况及感染控制效果。**结果** CRKP 造成的医院获得性血流感染共 6 例, 罹患率 1.29%(6/464), 与 2021 年同期(0)相比增高, 差异有统计学意义($P=0.011$)。环境卫生学监测中, CRKP 检出率为 2.27%(1/44), 来自感染患者居住床单元床帘表面, 与 2 例患者检出的 CRKP 进行同源性分析发现, 3 株 CRKP 的 16s RNA 完全相同, 相似度 100%; 3 株 CRKP 的 7 个管家基因均相同, 均属 ST11 型。采取综合控制措施: 适当关闭病区、集中隔离患者、病区终末消毒、固定医务人员并相对限制其活动区域, 采取措施后病区微生物菌落数合格率较采取措施前提高(2.27% VS 68.89%), 差异有统计学意义($P<0.001$), 且干预后未再出现 CRKP 感染病例, 控制措施有效。**结论** 本次暴发事件由我国常见 CRKP 中的 ST11 型引起, 层流床帘是病原菌传播的载体。推测清洁消毒不规范、手卫生执行不到位是传播的主要原因。而采用适当关闭病区策略、集中隔离患者能快速有效阻止传播蔓延。

[关键词] 医院感染; 暴发; 耐碳青霉烯类肺炎克雷伯菌; 血液科; CRKP; 血液肿瘤

[中图分类号] R181.3[†]2

Investigation and control of a suspected outbreak of carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection in patients with hematological tumors

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[Abstract] **Objective** To investigate a suspected outbreak of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) healthcare-associated bloodstream infection (HA-BSI), provide reference for effective control of CRKP infection. **Methods** The characteristics of CRKP infected patients and the risk factors for the event transmission in an adult hematology department of a teaching hospital in June 2022 were obtained by field epidemiological investigation. The specimens of environmental target strains were co-lected by blood nutrient agar inoculation, the removal status of environmental microorganisms and the effect of infection control after implementing control measures were compared. **Results** There were a total of 6 cases of CRKP HA-BSI, with an attacking rate of 1.29% (6/464), which was significantly higher than 0 during the same period in 2021, and difference was statistically significant ($P=0.011$). In environmental hygiene monitoring, the detection rate of CRKP was 2.27% (1/44), which was from the

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surface of bed curtain in the living unit of infected patients, homology analysis with CRKP detected from 2 patients revealed that the 16s RNA of 3 CRKP strains was completely identical, with a similarity of 100%. Seven house-keeping genes of 3 CRKP strains were all identical and belonged to the ST11 type. Comprehensive control measures were taken: appropriate closure of the ward, centralized isolation of patients, terminal disinfection of the ward, regular health care workers and relative restriction of their activity areas. After the measures were taken, the qualified rate of microbial colony count in the ward increased compared to before taking the measures (2.27% vs 68.89%, $P < 0.001$), with a statistically significant difference, there were no more CRKP infected cases after the intervention, indicating that the control measures were effective. **Conclusion** This outbreak was caused by ST11 type of common CRKP in China, and laminar bed curtains are carriers of pathogen transmission. It is speculated that non-standard cleaning and disinfection, as well as inadequate implementation of hand hygiene are the main causes for transmission. Adopting an appropriate strategy of closing the ward and concentrating patient isolation can quickly and effectively prevent the transmission of the event.

[Key words] healthcare-associated infection; outbreak; carbapenem-resistant *Klebsiella pneumoniae*; hematology department; CRKP; hematological tumor

随着耐碳青霉烯类肺炎克雷伯菌(carbapenem-resistant *Klebsiella pneumoniae*, CRKP)检出率不断上升^[1-2],其已成为全球优先预防与控制的耐药菌之一^[3],并为临床治疗和医院感染预防与控制带来巨大挑战。研究^[4]显示,医疗机构内 CRKP 的定植/感染常通过接触传播,以医务人员、患者、共用的医疗设备及病区环境为媒介造成交叉传播,有抗菌药物使用史、接受侵入性操作和外科手术、入住重症监护病房(ICU)及免疫功能低下的患者是感染的高风险人群^[5-6]。在我国,CRKP 造成的医院感染多报道于 ICU、神经内科和新生儿病房^[7-9]。血液肿瘤患者作为 CRKP 感染的高危人群,预防与控制感染的发生,降低其感染和病死率对临床具有重要意义^[10-11]。本研究就某教学医院成人血液肿瘤科 2022 年 6 月 CRKP 感染疑似暴发事件进行流行病学调查、环境卫生学监测,并分析感染的高危因素,采取一系列干预措施,最终得到有效控制。本研究旨在为血液系统疾病患者 CRKP 医院感染的预防与控制提供参考。

1 对象与方法

1.1 研究对象 2022 年 6 月 10—30 日某教学医院成人血液肿瘤科血标本检出 CRKP 的 6 例血液肿瘤科患者及同期入院的其他患者,共 464 例。

1.2 方法

1.2.1 流行病学调查及应急处置 依据《医院感染暴发与控制指南》(WS/T 524—2016)^[12]和《医院感染诊断标准(试行)》(2001 年)^[13]中关于败血症的判定,参照现场调查表及事件控制程序实施应急处置,

即病例判定和诊断核实。

1.2.2 指标计算 医院感染罹患率 = 短时间内科室医院感染的患者数/同期在科患者数 $\times 100\%$; CRKP 医院感染罹患率 = 短时间内科室 CRKP 感染患者数/同期在科患者数 $\times 100\%$ 。

1.2.3 环境目标菌监测 依据美国疾病控制与预防中心(CDC)2010 年《环境清洁评价方法》^[14]中关于高频接触位点的定义,将本次事件环境监测位点分为 3 部分:(1)患者部分,包括床栏、床头柜、输液架、呼叫铃等;(2)卫生间区域,含水槽、灯开关、门把手等;(3)公共区域,含监护仪表面、B 超机操作面板、空调开关等。调查小组分别于终末消毒前(6 月 28 日)及终末消毒后(7 月 2 日)对上述点位进行现场采样。采样方法为使用浸有生理盐水的无菌纤维拭子对物体表面进行最大面积涂抹,现场接种于血营养琼脂培养基上,立即送微生物实验室进行细菌培养和鉴定。菌落数卫生标准参照《医院消毒卫生标准》中 II 类环境要求(≤ 5.0 CFU/cm²)。

1.2.4 病原学鉴定及药敏试验 使用 VITEK MS 全自动微生物分析系统和 Clin-To F-II 飞行时间质谱仪进行菌株鉴定,VITEK 2 全自动微生物分析系统和 K-B 纸片扩散法进行药敏试验,按标准进行结果判读^[15]。

1.2.5 同源性分析 将仅留存的检出 CRKP 的 2 例患者血标本与环境 CRKP 检测阳性标本外送第三方生工生物工程(上海)有限公司进行 16s RNA 及多位点序列分型(MLST)测序,分析其同源性。16s RNA 分析网站: <https://blast.ncbi.nlm.nih.gov/Blast.cgi>; MLST 分析网站: <https://bigsd.bpasteur.fr/klebsiella/>。

1.3 统计分析 应用 SPSS 27.0 统计软件进行数据分析。检验资料是否符合正态分布采用 P-P 图, 计量资料比较采用 *t* 检验或秩和检验, 计数资料比较采用卡方检验或 Fisher 确切概率法。 $P \leq 0.05$ 为差异具有统计学意义。

2 结果

2.1 疑似医院感染暴发判定 2022 年 6 月 10—30 日 CRKP 导致的医院获得性血流感染罹患率为 1.29%(6/464), 较 2021 年同期(0,0/513)高, 差异有统计学意义($P = 0.011$)。核实为一起 CRKP 血流感染疑似医院感染暴发事件。

2.2 流行病学调查

2.2.1 人群分布 本事件中感染患者血培养检出的 CRKP, 经药敏试验结果提示耐药表型完全一致, 仅对替加环素、黏菌素敏感。6 例患者中, 女性 4 例(66.67%), 男性 2 例(33.33%); 平均年龄中位数 47 岁; 血液科住院时间中位数 25 d。患者住院期间均出现发热, 6 例患者均使用过碳青霉烯类抗生素, 本次在院期间未进行化学治疗(化疗); 1 例转科, 其余 5 例均留院治疗。6 例患者中, 1 例患者存在中心静脉置管, 医院感染诊断为中心静脉导管相关血流感染(CLABSI), 5 例医院感染感染诊断为非 CLABSI 血流感染, 见表 1。

表 1 6 例 CRKP 医院感染患者基本特征

Table 1 Basic characteristics of 6 patients with CRKP HAI

病例	年龄(岁)	性别	床号	入院诊断	住院时间(d)	抗菌药物使用时间(d)	发热时间(d)	使用碳青霉烯类抗生素	化疗	存在侵入性操作	医院感染诊断	转归
1	48	女	87	急性白血病, 急性髓系白血病	8	8	2	是	否	经皮深静脉置管	CLABSI	转科
2	26	女	71	急性白血病	25	14	11	是	否	否	血流感染	出院
3	44	女	85	急性髓系白血病	26	6	3	是	否	否	血流感染	出院
4	62	男	79	套细胞淋巴瘤, 非霍奇金淋巴瘤	28	27	7	是	否	否	血流感染	出院
5	61	男	77	急性髓系白血病	22	15	11	是	否	否	血流感染	出院
6	46	女	77	急性髓系白血病	29	11	7	是	否	否	血流感染	出院

2.2.2 时间分布 2022 年 6 月 11 日微生物实验室报告首例血培养检出 CRKP 患者, 此后 6 月 17、25、30 日各有 1 例患者血标本检出同种病原菌, 23

日检出 2 例。患者住院及病例微生物标本培养 CRKP 分布见图 1。

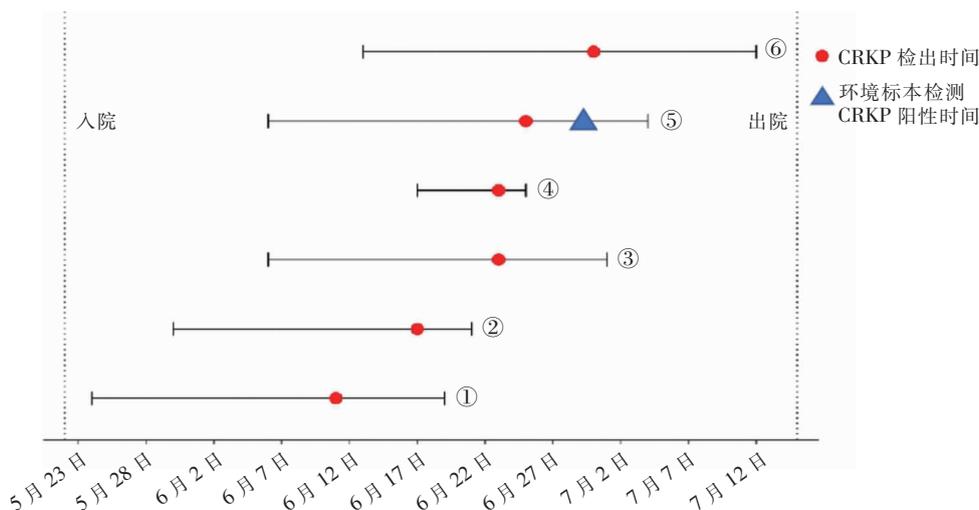


图 1 6 例 CRKP 血流医院感染病例及环境 CRKP 分离标本时间分布图

Figure 1 Time distribution of isolation of CRKP from 6 patients with CRKP HA-BSI and CRKP from environmental specimens

现死亡病例,虽然与 2019 年一项抗菌药物耐药性负担研究预测的高病死率结论有差异^[26],但究其原因,除了本次感染病例入院期间均未进行化疗、侵入性操作且感染均得到及时治疗外,不排除与耐药革兰阴性菌较革兰阳性菌所导致血流感染患者病死率更低有关^[27]。在本次事件传染源及传播途径的假设和验证中,发现最后 2 例 CRKP 感染患者的临床菌株与 6 月 28 日环境标本中检出的 CRKP 高度同源,虽然不能验证两者之间污染和被污染的因果关系,但反映了此次暴发事件存在 CRKP 通过患者床单元环境在病区传播的可能,层流床床帘外表面的清洁消毒工作不容忽视,尤其收治多重耐药菌感染患者时更应加强清洁消毒。

鉴于 CRE 感染导致的严重后果,世界卫生组织(WHO)等已针对 CRE 医院感染防控提出一系列集束化感染控制干预策略^[2-3],包括对患者开展定植/感染的主动筛查(肛/咽拭子),集中或单间预防性隔离患者,提高手卫生依从性,避免转院,环境清洁消毒,环境中 CRE 的定植和污染筛查,减少侵入性操作和患者去定植等。但与 WHO 建议不同,在中国专家共识中,患者 CRE 去定植、环境消毒并未纳入推荐措施^[24]。这表明适用于中国血液肿瘤患者的 CRE 防控措施还有待探讨。本研究除借鉴上述措施外,还固定并相对限制本病区医务人员流动,并实施了“关闭病区”策略,这在一定程度上能最大限度控制暴发事态^[28],在本次事件中快速、有效扼制了病区内 CRKP 的传播。

本研究也存在一定局限性。一是仅对部分发热患者进行肛拭子 CRKP 筛查,不能为本次调查提供分析依据。二是采取控制措施时,在病区使用过氧化氢喷雾进行终末消毒时消毒次数为 3 次,是否存在消毒剂过量使用及其对患者产生的潜在影响有待进一步论证。关于终末消毒措施,部分研究^[28-30]认为多重耐药菌的防控不需提高消毒剂浓度,而是依靠增加清洁消毒频次来保证病原体能够被有效消除;也有研究^[31-32]表示因表面消毒剂能有效抑制环境中的多重耐药菌,只要严格落实常规清洁消毒即可消除环境中的 CRE;而血液肿瘤患者 CRE 感染的诊治与防控中国专家共识^[24]也仅将环境清洁作为强推荐措施,未强调消毒的必要性。由此可见,该措施仍未有统一定论。三是“适当关闭病区”策略虽能控制感染传播速度,但其所带来的后果如医疗资源不能迅速补充,无疑也对医疗机构带来冲击^[28],其使用指征基于病原体的传播方式和患者的基础情

况,适用性有待探讨。四是未能保留所有患者的临床标本进行源性分析,以进一步验证环境污染是本次事件发生主要原因的假设。

鉴于研究者所在部门无独立检验设备,故本研究委托第三方进行源性基因鉴定,未能呈现分型结果;且采取的多模式防控措施与部分研究有差异,在后续研究中,将对血液科高危患者开展主动监测和筛查,寻找并控制感染高危因素,防止病原体在医疗机构,尤其是血液科等重点部门内传播。

利益冲突:所有作者均声明不存在利益冲突。

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