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◇临床医学研究◇

肺部多耐药大肠埃希菌感染患者合并活动性结核病的因素分析

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摘要 目的 分析肺部多重耐药大肠埃希菌(MDR-ECO)感染患者合并活动性结核病(ATB)的影响因素。**方法** 收集肺部感染 MDR-ECO 的住院患者 204 例,其中合并 ATB 患者共 89 例为观察组,使用单因素分析及多因素 Logistic 回归分析筛选出肺部 MDR-ECO 感染患者合并 ATB 的危险因素。**结果** 患者年龄、中性粒细胞数、血红蛋白、活动性恶性肿瘤、类风湿关节炎、抗生素暴露史、1 年内手术史等均是肺部 MDR-ECO 感染患者合并 ATB 的影响因素(均 $P<0.05$),其中高龄(95% CI:0.949 ~ 0.992,$P=0.008$)、中性粒细胞降低(95% CI:0.750 ~ 0.922,$P<0.001$)、抗生素暴露史(95% CI:1.202 ~ 2.596,$P=0.004$)是独立危险因素。**结论** 部分肺部 MDR-ECO 感染患者易合并 ATB,应加强对高龄、中性粒细胞数少、既往有抗生素暴露史的高危患者进行 ATB 筛查。

关键词 肺部感染;多重耐药大肠埃希菌;活动性结核病;影响因素;危险因素;筛查

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大肠埃希菌是正常肠道菌群,然而,一些大肠埃希菌可在人类、其他哺乳动物和鸟类中致病,从肠内感染到肠外[1]。致病性大肠埃希菌在发病率和死亡率方面对公共卫生影响巨大,每年消耗全球经济成本为数十亿美元[2]。有研究[3]发现,细菌感染与结核聚合酶链反应阳性患者 2 周死亡风险增加显著相关。临床工作中发现很多肺部多重耐药大肠埃希

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PCV13 for children born in 2017—2023 from the Anhui Immunization Information Management System. We estimated coverage levels and described characteristics of coverage. The spatial autocorrelation analysis of coverage was conducted. ***Results*** Cumulative coverage, cumulative primary immunization coverage and cumulative full-series coverage of PCV13 were 17.19%, 12.12% and 9.09% among the 2017—2023 birth cohort in Anhui Province. The coverage of PCV13 increased from 1.14% in the 2017 birth cohort to 41.59% in the 2022 birth cohort. The first dose of PCV13 at ages under 3, 3—6, 7—11, 12—23 and not less than 24 months were 45.35%, 29.84%, 5.52%, 10.75% and 8.53%, respectively. There were significant differences in the ages of the first dose between children of different years of born and kinds of PCV13 ($P<0.001$). Significant differences were also observed in the cumulative coverage, cumulative primary immunization coverage, cumulative full-series coverage of PCV13 and ages of the first dose among children from various residence regions ($P<0.001$). From 2018 to 2023 birth cohort, the coverage of PCV13 in Anhui Province showed obvious positive spatial autocorrelation. Local spatial autocorrelation analysis showed that the "high-high" agglomeration areas were concentrated in the central area of Anhui. ***Conclusion*** The coverage of PCV13 was low in Anhui Province with significant regional differences.

Key words 13-valent pneumococcal conjugate vaccine; vaccination; coverage; children; birth cohort; spatial analysis

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菌(multi-drug resistant *Escherichia coli*,MDR-ECO)感染患者合并活动性结核病(active tuberculosis,ATB),此类患者预后欠佳。然而结核病早期症状不典型,全球诊断率低,病例发现率不高(2021 年有病原学依据的为 63%[4])。肺部 MDR-ECO 感染患者中,有许多潜在合并 ATB 的患者难以发现,漏诊漏治疗均对患者病情恢复不利,增加病死率。该研究回顾性分析了 89 例肺部 MDR-ECO 感染患者合并 ATB 的临床特点,并分析合并 ATB 的相关危险因素,以便早期发现,及早调整诊疗策略,改善患者的临床预后,减轻经济负担,降低病死率。

1 材料与方法

1.1 研究对象 选择 2020 年 1 月—2023 年 4 月安徽省胸科医院肺部感染患者中送检的痰、灌洗液标本培养出 MDR-ECO 的住院患者 204 例,其中合并 ATB 患者 89 例为观察组,未合并 ATB 患者 115 例为对照组。纳入标准:① 筛选出胸部影像学检查确定肺部活动性病灶者;② 痰、灌洗液中培养出 MDR-ECO,并符合多重耐药标准,合并或无合并结核病;③ 肺结核诊断符合《中华人民共和国卫生行业标准 肺结核诊疗诊断》(WS288-2017)标准;④ 年龄 >18 岁,性别无限制。排除标准:① 痰、灌洗液检出除大肠埃希菌、结核分枝杆菌外其他细菌者;② 临床资料不完整者;③ 不愿意参加该研究项目者。本研究通过安徽省胸科医院伦理委员会审核批准(批准号:K2023-024),所有患者均知情同意,并签署知情同意书。

1.2 方法

1.2.1 资料收集 收集两组患者的临床资料,主要包括患者年龄、性别、住院时间、血清白蛋白、中性粒细胞数、血红蛋白、C 反应蛋白、血小板数、淋巴细胞百分比、患者共病情况、抗生素暴露史、1 年内手术史、培养出大肠埃希菌药敏情况等临床资料。

1.2.2 病原菌培养与药敏试验 使用 BD phoenix™ M50 全自动微生物鉴定系统(美国 BD 公司)MIC 法或纸片扩散法(英国赛默飞世尔科技有限公司)对所鉴定的菌株进行药敏试验,药敏结果判断参照美国临床和实验室标准化协会推荐药敏判读标准[5]。

1.3 统计学处理 使用 SPSS 26.0 软件进行数据分析,对于符合正态分布的计量资料用 $\bar{x} \pm s$ 表示,两组间的比较采用 t 检验,对于非正态分布的计量资料用 $M(Q1,Q3)$ 表示,两组间的比较采用非参数检验。计数资料用 $n(\%)$ 表示,用 χ^2 检验比较分布有无差异。将单因素分析中有意义的变量进行 Logistic 逐步回归分析。$P<0.05$ 为差异有统计学意义。

2 结果

2.1 肺部 MDR-ECO 感染患者合并 ATB 的影响因素分析 单因素分析显示,两组患者的年龄、中性粒细胞数、血红蛋白、活动性恶性肿瘤、类风湿关节炎、瘘、抗生素暴露史、1 年内手术史、气管切开、留置胃管、留置尿管均是肺部 MDR-ECO 感染患者合并 ATB 的影响因素,组间比较差异有统计学意义($P<0.05$),见表 1 ~4。对上述因素进行多因素 Logistic 逐步回归分析得出,高龄、中性粒细胞数少、抗生素暴露史为肺部 MDR-ECO 感染患者合并 ATB 的独立危险因素($P<0.05$),见表 5。

表 1 肺部 MDR-ECO 感染患者合并 ATB 的一般情况的单因素分析

Tab.1 Univariate analysis of the general status of ATB in patients with pulmonary MDR-ECO infection

Variable	Control group (n=115)	Observation group (n=89)	$\chi^2/Z/t$ value	P value
Gender[n(%)]			1.721	0.190
Male	84 (73.04)	72 (80.90)		
Female	31 (26.96)	17 (19.10)		
Age(year, $\bar{x} \pm s$)	67.36 ± 13.49	61.63 ± 14.33	-2.919	0.004
Age group [n(%)]			14.214	0.023
26 -35	5 (4.35)	6 (6.74)		
>35 -45	0 (0)	5 (5.62)		
>45 -55	14 (12.17)	18 (20.22)		
>55 -65	26 (22.61)	14 (15.73)		
>65 -75	40 (34.78)	34 (38.20)		
>75 -85	22 (19.13)	8 (8.99)		
>85	8 (6.96)	4 (4.49)		
Length of stay [d, $M(Q1,Q3)$]	16.00 (11.00,27.00)	13.00 (10.00,20.00)	-1.960	0.050

2.2 肺部 MDR-ECO 感染患者的耐药情况分析 合并 ATB 的患者培养出的 MDR-ECO 对氯霉素耐药率大于未合并者,差异有统计学意义($P<0.05$);合并 ATB 的患者培养出的 MDR-ECO 对亚胺培南($P<0.05$)、美罗培南($P<0.05$)的耐药率小于未合并 ATB 者,差异有统计学意义,见表 6。

3 讨论

多重耐药菌是指对 3 种及 3 种以上抗生素耐药的细菌,其中大肠埃希菌为常见多重耐药菌之一。越来越多临床工作中发现肺部MDR-ECO感染患者

表 2 肺部 MDR-ECO 感染患者合并 ATB 的实验室检查结果的单因素分析

Tab. 2 Univariate analysis of laboratory results of pulmonary MDR-ECO infection in patients with ATB

Variable	Control group (n = 115)	Observation group (n = 89)	Z/t value	P value
Serum albumin (g/L, $\bar{x} \pm s$)	31.17 ± 4.68	31.29 ± 5.68	−0.156	0.877
Neutrophil count [$\times 10^9$/L, $M(Q1,Q3)$]	5.56 (3.87,8.58)	3.89 (2.82,5.70)	−4.390	<0.001
C-reactive protein [pg/ml, $M(Q1,Q3)$]	32.18 (8.32,90.40)	24.47 (5.68,60.64)	−1.420	0.156
Hemoglobin (g/L, $\bar{x} \pm s$)	107.57 ± 20.92	101.31 ± 19.70	2.171	0.031
Platelet count ($\times 10^9$/L, $\bar{x} \pm s$)	229.18 ± 106.64	236.20 ± 111.68	−0.457	0.648
Percentage of lymphocytes (%, $\bar{x} \pm s$)	16.17 ± 9.84	18.58 ± 10.56	−1.678	0.095

表 3 肺部 MDR-ECO 感染患者合并 ATB 的共病情况的单因素分析[n(%)]

Tab. 3 Univariate analysis of comorbidity of ATB in patients with pulmonary MDR-ECO infection [n(%)]

Variable	Sort	Control group (n = 115)	Observation group (n = 89)	χ^2 value	P value
Active malignant tumor	No	76(66.09)	85(95.51)	26.102	<0.001
	Yes	39(33.91)	4(4.49)		
Chronic obstructive pulmonary disease	No	97(84.35)	73(82.02)	0.195	0.659
	Yes	18(15.65)	16(17.98)		
Bronchiectasis	No	100(86.96)	77(86.52)	0.008	0.927
	Yes	15(13.04)	12(13.48)		
Interstitial pneumonia	No	109(94.78)	85(95.51)	0.056	0.813
	Yes	6(5.22)	4(4.49)		
Rheumatoid arthritis	No	115(100.00)	85(95.51)	5.272	0.022
	Yes	0(0)	4(4.49)		
Lung abscess	No	112(97.39)	89(100.00)	2.356	0.125
	Yes	3(2.61)	0(0)		
Pulmonary aspergillosis	No	109(94.78)	88(98.88)	2.538	0.111
	Yes	6(5.22)	1(1.12)		
Diabetes	No	100(86.96)	72(80.90)	1.392	0.238
	Yes	15(13.04)	17(19.10)		
Hypertension	No	87(75.65)	68(76.40)	0.016	0.901
	Yes	28(24.35)	21(23.60)		
Cardiovascular and cerebrovascular diseases	No	75(65.22)	63(70.79)	0.711	0.399
	Yes	40(34.78)	26(29.21)		
Fistula	No	98(85.22)	85(95.51)	5.751	0.016
	Yes	17(14.78)	4(4.49)		
Respiratory failure	No	112(97.39)	84(94.38)	1.206	0.272
	Yes	3(2.61)	5(5.62)		
Chronic hepatitis	No	112(97.39)	83(93.26)	2.032	0.154
	Yes	3(2.61)	6(6.74)		

有不少存在合并 ATB 情况,发现延误可导致住院时间延长,经济负担加重,病死率增加,因此了解肺部 MDR-ECO 感染患者合并 ATB 的危险因素意义重大。

本研究显示,肺部 MDR-ECO 感染患者合并 ATB 者年龄分布中,65 岁以上感染人数占比 51.68%,其中 >65 ~75 岁感染人群最高,考虑属于易感年龄段。结核分枝杆菌接触肺泡后对肺泡内衬液环境有反应,由年龄等因素决定的宿主的肺泡内衬液体状态,可能在决定感染结局中发挥重要作用[6]。一项针对 2004—2019 年中国结核病报告和病死率研究[7]发现,60 岁以上的老年人为结核病死亡的风险人群。故对于高龄的肺部 MDR-ECO 感染患者,需加强对 ATB 的筛查,以免漏诊而延误治疗,导致死亡。

本研究中,淋巴细胞百分比与肺部 MDR-ECO 感染合并 ATB 无关联,中性粒细胞减少为独立危险因素,中性粒细胞数量与结核病风险之间存在负相关关系。研究显示,中性粒细胞在感染阶段会介导病理变化和疾病进展[8],导致合并 ATB 患者的组织损伤,造成更加严重的临床表现[9]。然而,在受细菌等刺激后,中性粒细胞开始释放细胞外诱捕网,介导许多免疫反应,在结核分枝杆菌感染过程中,包围、限制细菌,并与巨噬细胞相互作用,帮助清除结

表 4 肺部 MDR-ECO 感染患者合并 ATB 的治疗情况的单因素分析[*n*(%)]

Tab. 4 Univariate analysis of treatment of pulmonary MDR-ECO infection in patients with ATB [*n*(%)]

Variable	Sort	Control group (*n* = 115)	Observation group (*n* = 89)	χ^2 value	*P* value
History of glucocorticoid use	No	87(75.65)	71(79.78)	0.488	0.485
	Yes	28(24.35)	18(20.22)		
History of antibiotic exposure	No	30(26.09)	11(12.36)	7.839	0.020
	<7 d	23(20.00)	14(15.73)		
	≥7 d	62(53.91)	64(71.91)		
History of surgery within 1 year	No	95(82.61)	83(93.26)	5.117	0.024
	Yes	20(17.39)	6(6.74)		
Tracheotomy	No	107(93.04)	88(98.88)	4.048	0.044
	Yes	8(6.96)	1(1.12)		
Tracheal intubation	No	110(95.65)	87(97.75)	0.668	0.414
	Yes	5(4.35)	2(2.25)		
Sputum aspiration	No	105(91.30)	87(97.75)	3.768	0.052
	Yes	10(8.70)	2(2.25)		
Indwelling PICC tube	No	111(96.52)	89(100.00)	3.158	0.076
	Yes	4(3.48)	0(0)		
An indwelling gastric tube	No	96(83.48)	89(100.00)	16.215	0.000
	Yes	19(16.52)	0(0)		
An indwelling catheter	No	101(87.83)	88(98.88)	8.993	0.003
	Yes	14(12.17)	1(1.12)		
Indwelling thoracic and (or) abdominal drainage tube	No	108(93.91)	86(96.63)	0.794	0.373
	Yes	7(6.09)	3(3.37)		

表 5 肺部 MDR-ECO 感染患者合并 ATB 的多因素 Logistic 回归分析

Tab. 5 Multivariate Logistic regression analysis of ATB in patients with pulmonary MDR-ECO infection

Variable	*β*	SE	Wald χ^2	Degree of freedom	*P* value	*OR*	95% *CI*
Neutrophil count	−0.184	0.053	12.192	1	<0.001	0.832	0.750 − 0.922
Age	−0.030	0.011	7.042	1	0.008	0.971	0.949 − 0.992
History of antibiotic exposure	0.569	0.197	8.376	1	0.004	1.766	1.202 − 2.596

核分枝杆菌[10]。大多数感染结核的患者以 T 细胞向感染部位募集的方式控制结核分枝杆菌生长,以产生长期的保护性免疫[2]。然而也有研究[11]发现,中性粒细胞能够提高树突状细胞介导的 T 细胞应答。

抗生素暴露史加大了肺部 MDR-ECO 感染患者合并 ATB 的风险。一方面,抗生素的使用造成了选择性压力,推动结核分枝杆菌快速进化,通过连续积累,从单一耐药性发展到多重耐药性、广泛耐药性,并最终完全耐药性。即漫长的治疗过程中持续的抗生素暴露,促使进化选择耐药突变体[12]。另一方面,抗生素治疗可以破坏宿主微生物群的动态平衡。研究[13]发现,宿主微生物组稳态的扰动可以扰乱宿主的正常或健康状态。特别是,接触抗生素是改变人类微生物群组成的一个重要环境因素,在某些情况下,与患者的不良健康影响有关。

本研究结果也显示,肺部 MDR-ECO 感染患者中,合并 ATB 者对亚胺培南($P < 0.05$)、美罗培南($P < 0.05$)的耐药率小于未合并 ATB 者,差异有统计学意义,由于本研究样本量有限,故此项结果仍需进一步证实。但可以确定的是,根据本研究,对于肺部 MDR-ECO 感染患者,对碳青霉烯类抗生素总体耐药率不高,可依据药敏结果,优选选择碳青霉烯类抗生素。世界卫生组织将碳青霉烯类分为 V 组抗结核药物,也被称为三线药物。多耐药结核菌日渐泛滥,在开发新药的同时,对包括碳青霉烯类药物的重新利用和优化,是改善结核病治疗的合理策略[14]。因碳青霉烯能被结核分枝杆菌内的 β-内酰胺酶水解,近几年研究碳青霉烯类抗生素联合克拉维酸盐(一种 β-内酰胺酶抑制剂)治疗耐药肺结核开始增多。有研究[15]发现美罗培南和利福平联合应用能够很好地控制利福平敏感的结核分枝杆菌,而且这种联合治疗还能够有效抑制利福平耐药菌株的生长,从而达到良好的治疗效果。

本研究发现,肺部 MDR-ECO 感染患者部分易合并ATB,其中高龄、中性粒细胞数少、抗生素暴露

表 6 安徽省胸科医院肺部 MDR-ECO 感染患者耐药性分析[*n*(%)]

Tab. 6 Drug resistance analysis of patients with pulmonary MDR-ECO infection in Anhui Chest Hospital [*n*(%)]

Variable	Sort	Control group ($n=115$)	Observation group ($n=89$)	χ^2 value	*P* value
Amoxicillin/clavulanic acid	No drug resistance	84(73.04)	62(69.66)	0.282	0.596
	Drug resistance	31(26.96)	27(30.34)		
Amikacin	No drug resistance	108(93.91)	79(88.76)	1.741	0.187
	Drug resistance	7(6.09)	10(11.24)		
Aztreonam	No drug resistance	30(26.09)	24(26.97)	0.020	0.888
	Drug resistance	85(73.91)	65(73.03)		
Ceftazidime	No drug resistance	50(43.48)	47(52.81)	1.751	0.186
	Drug resistance	65(56.52)	42(47.19)		
Chloramphenicol	No drug resistance	52(45.22)	25(28.09)	6.263	0.012
	Drug resistance	63(54.78)	64(71.91)		
Ciprofloxacin	No drug resistance	10(8.70)	7(7.87)	0.045	0.831
	Drug resistance	105(91.30)	82(92.13)		
Cefoperazone/Sulbactam	No drug resistance	75(65.22)	61(68.54)	0.249	0.618
	Drug resistance	40(34.78)	28(31.46)		
Cefazolin	No drug resistance	1(0.87)	0(0)	0.778	0.378
	Drug resistance	114(99.13)	89(100.00)		
Cefepime	No drug resistance	34(29.57)	27(30.34)	0.014	0.905
	Drug resistance	81(70.43)	62(69.66)		
Gentamycin	No drug resistance	51(44.35)	37(41.57)	0.157	0.691
	Drug resistance	64(55.65)	52(58.43)		
Imipenem	No drug resistance	103(89.57)	87(97.75)	5.262	0.022
	Drug resistance	12(10.43)	2(2.25)		
Levofloxacin	No drug resistance	10(8.70)	8(8.99)	0.005	0.942
	Drug resistance	105(91.30)	81(91.01)		
Meropenem	No drug resistance	104(90.43)	87(97.75)	4.503	0.034
	Drug resistance	11(9.57)	2(2.25)		
Ampicillin/sulbactam	No drug resistance	54(46.96)	38(42.70)	0.368	0.544
	Drug resistance	61(53.04)	51(57.30)		
Cotrimoxazole	No drug resistance	35(30.43)	20(22.47)	1.616	0.204
	Drug resistance	80(69.57)	69(77.53)		
Tetracycline	No drug resistance	21(18.26)	12(13.48)	0.845	0.358
	Drug resistance	94(81.74)	77(86.52)		
Piperacillin/Tazobactam	No drug resistance	90(78.26)	68(76.40)	0.099	0.753
	Drug resistance	25(21.74)	21(23.60)		

史等是高危因素。本研究可在临床工作中为此类患者提高治愈率,缩短住院时间,减轻经济负担,降低病死率等提供一定的指导价值。但是本研究也有一定的不足之处,由于样本量有限,研究结果可能存在一定偏倚,期待后期研究扩充样本量进一步支撑该研究结果。另外本研究只涵盖了 MDR-ECO,临床工作中也发现其它多重耐药菌,例如肺炎克雷伯菌、铜绿假单胞菌、鲍曼不动杆菌等,后续研究拟纳入多种耐药细菌合并 ATB 病例进行纵向研究,以发现多种耐药菌合并 ATB 的临床特征及危险因素。

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Factor analysis of pulmonary multidrug-resistant *Escherichia* coli infection in patients with active tuberculosis

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Abstract ***Objective*** To analyze the influencing factors associated with the coexistence of multidrug-resistant *Escherichia coli* (MDR-ECO) infection and active tuberculosis (ATB) in patients with lung infections. ***Methods*** A total of 204 hospitalized patients with lung infections caused by MDR-ECO were enrolled. Among them, patients with coexisting ATB were identified and assigned to the observation group. Univariate and multivariate Logistic regression analysis were performed to identify the risk factors for the coexistence of MDR-ECO lung infection and ATB. ***Results*** Factors such as patient age, neutrophil count, hemoglobin level, malignancy, rheumatoid arthritis, history of antibiotic exposure, and history of surgery within the past year were found to be influencing factors for the coexistence of MDR-ECO lung infection and ATB (all $P < 0.05$). Specifically, advanced age (95% *CI*: 0.949 - 0.992, $P = 0.008$), decreased neutrophils (95% *CI*: 0.750 - 0.922, $P < 0.001$), and a history of antibiotic exposure (95% *CI*: 1.202 - 2.596, $P = 0.004$) were identified as risk factors. ***Conclusion*** Some patients with MDR-ECO lung infections are prone to coexisting with ATB. Therefore, it is recommended to strengthen ATB screening among high-risk patients, including those at peak ages for susceptibility, with low neutrophil counts, and with a history of antibiotic exposure.

Key words lung infection; multidrug resistant escherichia coli; active tuberculosis; influencing factors; risk factors; screening

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