

上海市耐多药结核病患者二线药物耐药情况及危险因素分析

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【摘要】 目的 分析上海市耐多药结核病(MDR-TB)患者二线药物耐药分布情况及危险因素。方法 收集2009年上海市各区(县)结核病定点医院痰培养阳性菌株,进行菌型鉴定和一线抗结核药物(异烟肼、利福平、链霉素及乙胺丁醇)敏感性检测,对耐多药菌株进行二线抗结核药物(卡那霉素、阿米卡星、卷曲霉素、氧氟沙星、对氨基水杨酸及丙硫异烟胺)敏感性检测,结合患者特征及实验室信息,采用多因素分析上海市MDR-TB患者二线药物耐药的危险因素。结果 2009年上海市确诊的1867例结核病病例中,112例(6.0%)为MDR-TB患者,其中58例(51.8%)至少耐1种二线抗结核药物,10例为广泛耐药结核病。多因素分析显示,MDR-TB患者中,45~59岁年龄组($aOR=4.76, P=0.001$)及痰涂片阳性($aOR=6.51, P=0.026$)与二线药物耐药相关。结论 上海市MDR-TB患者二线抗结核药物耐药情况严重,45~59岁年龄组和痰涂片阳性是MDR-TB患者二线药物耐药相关的危险因素。

【关键词】 耐多药结核病; 危险因素

Prevalence and risk factors on the resistance related to second-line drugs among multi-drug resistant tuberculosis cases in Shanghai, China Li Jing, ZHANG Yang-yi, GUI Xiao-hong, YUAN Zheng-an, PAN Qi-chao, MEI Jian, SHEN Xin. Shanghai Municipal Center for Disease Control and Prevention, Shanghai 200336, China

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【Abstract】 **Objective** To determine the prevalence and risk factors on second-line drug resistance in patients with multidrug resistant tuberculosis (MDR-TB) in Shanghai, China. **Methods** All pulmonary TB patients with sputum culture positivity detected in Shanghai during January to December, 2009, were enrolled. All of the pretreatment sputum-positive cultures samples were tested for routine specimen identification and routine drug susceptibility testing for first-line drugs (Isoniazid, Rifampin, Ethambutol and Streptomycin). Drug susceptibility testing on second-line anti-TB drugs (Ofloxacin, Amikacin, Kanamycin, Capreomycin, P-aminosalicylic acid and Prothionamide) was routinely performed on isolates of *Mycobacterium (M.) TB* with MDR. Logistic regression analysis was conducted to determine the risk factors regarding second-line drug resistance. **Results** A total of 1867 patients infected with *M. TB* isolates were diagnosed at the TB hospitals/clinics in Shanghai during the study period, of whom 112 (6.0%) were MDR-TB, in which 58 cases (51.8%) showed resistant to at least one of the second-line drugs tested and 10 cases belonged to extensively drug-resistant. In the multivariate analyses, MDR-TB patients who were aged 45-59 years ($aOR=4.76, P=0.001$), with sputum smear positivity ($aOR=6.51, P=0.026$) were significantly more likely to show resistance to second-line drugs. **Conclusion** The prevalence of second-line drug resistance among MDR-TB patients was high in Shanghai. MDR-TB patients who were under age of 45-59 years and with sputum smear positivity would represent important common risk factors for the resistance to second-line drugs.

【Key words】 Multidrug resistant tuberculosis; Risk factors

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耐多药结核病(MDR-TB)是指至少同时对异烟肼和利福平耐药的结核病^[1]。MDR-TB患者需要使用二线抗结核药物治疗^[2],其使用导致广泛耐药结核病(XDR-TB)的出现,给结核病有效控制带来严重挑战^[3-6]。由于不同地区结核病的流行病学、研究人群、二线抗结核药物的实际使用等存在差异,因此MDR-TB患者的二线抗结核药物耐药率也存在差异^[3,5-7]。2000—2006年上海市肺结核病患者流行病学调查结果表明MDR-TB患者占4.0%^[8],且出现对二线抗结核药物耐药的患者^[9,10]。本研究对2009年上海市MDR-TB患者二线抗结核药物耐药现状及危险因素进行分析。

对象与方法

1. 研究对象:2009年1—12月上海市所有区(县)结核病定点医院确诊的痰培养阳性的肺结核患者,将治疗前首次分离的菌株送上海市疾病预防控制中心结核病参比实验室进行菌种鉴定和一线抗结核药物(异烟肼、利福平、链霉素和乙胺丁醇)敏感性检测,根据一线抗结核药物耐药情况,选择MDR-TB患者作为研究对象,对其痰分离菌株进行二线抗结核药物敏感性检测。

2. 研究方法:药敏试验参照文献^[11],采用WHO推荐的1%标准比例法(标准接种环稀释法)进行二线抗结核药敏检测^[12](括号内数据为药物终浓度):氧氟沙星(OFX, 2 μg/ml)、阿米卡星(AM, 40 μg/ml)、卡那霉素(KM, 30 μg/ml)、卷曲霉素(CM, 40 μg/ml)、对氨基水杨酸钠(PAS, 1 μg/ml)和丙硫异烟胺(PTH, 40 μg/ml)。

3. 统计学分析:采用Foxpro 6.0软件整理流行病学资料。统计学分析采用Stata 8.0软件。组间分布差异采用 χ^2 检验或Fisher's精确检验, $P < 0.05$ 为差异有统计学意义。采用单因素和多因素分析以识别至少耐1种二线药物的危险因素,评价比值比(OR)和95%可信区间(CI)。2×2表单因素分析中, $P < 0.20$ 的变量选入非条件logistic多因素回归分析。候选变量的筛选采用前进法,依次比较每个模型的对数似然比。

结 果

1. 基本情况:2009年1—12月上海市各区(县)结核病定点医院共报告确诊肺结核病患者4380例,2141例(48.9%)的痰标本经培养为阳性,对2040份菌株进行菌种鉴定,1867份(91.5%)为结核分枝杆菌,经一线抗结核药物耐药检测,112例(6.0%)患者为MDR-TB,其中男性84例(75.0%),女性28例

(25.0%),年龄中位数44(14~84)岁;初治患者58例(51.8%),复治患者54例(48.2%)。

2. 二线抗结核药物耐药情况:112例MDR-TB患者中,58例(51.8%)对6种二线药物中至少1种具有耐药性,初治患者的二线药物耐药率为44.8%(26/58),复治患者的二线药物耐药率为59.3%(32/54);6种二线药物中,OFX耐药率最高,达38.4%(43/112),其中初治患者和复治患者各占29.3%、48.1%;3种注射类药物(KM、CM、AM)耐药率8.0%~14.3%,PAS耐药率为13.4%(15/112),PTH耐药率最低为4.5%(5/112)。10例(8.9%)为XDR-TB,包括6例(10.3%)初治和4例(7.4%)复治患者(表1)。

表1 2009年上海市MDR-TB患者的
二线抗结核药物耐药情况

耐二线药物	合计 (n=112)	MDR-TB患者	
		初治(n=58)	复治(n=54)
≥1种	58(51.8)	26(44.8)	32(59.3)
OFX	43(38.4)	17(29.3)	26(48.1)
KM	16(14.3)	11(19.0)	5(9.3)
CM	10(8.9)	6(10.3)	4(7.4)
AM	9(8.0)	6(10.3)	3(5.6)
PAS	15(13.4)	10(17.2)	5(9.3)
PTH	5(4.5)	0	5(9.3)
XDR	10(8.9)	6(10.3)	4(7.4)

注:括号外数据为耐药人数,括号内数据为耐药率(%)

对MDR-TB患者的二线抗结核药物耐药表型谱分析结果显示,单耐OFX较常见,为25.0%(28/112),其次是单耐PAS,为6.3%(7/112),单耐KM为5.4%(6/112)。初治和复治患者均以单耐二线抗结核药物为主,占37.5%(42/112),在MDR-TB患者中耐2种以上二线抗结核药物占13.4%(15/112),较为常见的耐药组合形式是OFX+KM+AM+CM,为3.6%(4/112),及OFX+KM+AM+CM+PAS,占2.7%(3/112),1例患者对6种二线抗结核药物耐药。

3. MDR-TB患者二线抗结核药物耐药危险因素分析:单因素分析结果显示二线药物耐药危险因素包括45~59岁年龄组(OR=5.33, $P=0.0018$)、痰涂片阳性(OR=6.36, $P=0.0133$)、本市户籍居民(OR=2.56, $P=0.0146$)。见表2。

logistic多因素回归分析结果显示,与二线药物耐药相关因素有45~59岁年龄组(aOR=4.76, 95%CI:1.96~11.59, $P=0.001$)、痰涂片阳性(aOR=6.51, 95%CI:1.25~33.82, $P=0.026$)。

讨 论

MDR-TB患者的治疗成功与否取决于二线抗结核药物组合的选择^[2]。本研究中51.8%的MDR-TB

表2 2009年上海市MDR-TB二线药物耐药危险因素单因素分析

变量	耐至少1种二线药物				OR值(95%CI)	P值
	耐药		敏感			
	人数	构成比(%)	人数	构成比(%)		
性别						
女	11	39.3	17	60.7	1	
男	47	56.0	37	44.0	1.96(0.75~5.22)	0.1264
年龄(岁)						
14~	9	36.0	16	64.0	1	
30~	12	38.7	19	61.3	1.12(0.33~3.86)	0.8351
45~	30	75.0	10	25.0	5.33(1.59~18.24)	0.0018
60~	7	43.7	9	56.3	1.38(0.32~5.95)	0.6197
抗结核治疗史						
初治	26	44.8	32	55.2	1	
复治	32	59.3	22	40.7	1.79(0.79~4.06)	0.1267
痰涂片						
阴性	2	16.7	10	83.3	1	
阳性	56	56.0	44	44.0	6.36(1.24~61.75)	0.0133
户籍						
流动人口	21	39.6	32	60.4	1	
本市居民	37	62.7	22	37.3	2.56(1.12~5.90)	0.0146
居住区域						
郊区	34	47.2	38	52.8	1	
市区	24	60.0	16	40.0	1.68(0.71~3.97)	0.1947

患者至少对1种二线抗结核药物耐药,13.5%的MDR-TB患者耐≥2种二线药物,还有1例患者对6种二线药物耐药。由于能获得的二线抗结核药物种类非常有限,二线药物耐药的高度流行提示必须加强对其规范使用的监督。

有研究表明老年结核病患者更易伴有并发症,使用一线抗结核药物会产生肝功能损害、胃肠道反应、过敏等药物不良反应^[13,14],因此可能会更多地选择二线抗结核药物,从而导致二线药物耐药。本研究结果表明,45~59岁年龄组的MDR-TB患者与二线药物耐药相关,然而,年龄在60岁以上的老年结核病患者与二线药物耐药并没有显著关联(虽然该年龄组的患者比30岁以下年龄组的患者具有更高的耐药率),这可能与样本量不足有关。

本研究中,痰涂片阳性MDR-TB患者对二线抗结核药物耐药率是涂片阴性患者的6倍。已有研究显示XDR-TB患者的痰涂片阳性率显著高于MDR-TB患者^[15]。由于痰涂片阳性患者具有一定的传染性,且MDR-TB或XDR-TB患者的传染周期更长^[7],所以早期发现、诊断和治疗MDR-TB/XDR-TB患者迫在眉睫。

已有研究显示复治是耐药的危险因素^[5,16],而在本研究中并未发现复治与二线药物耐药相关。以往认为复治是导致治疗失败而产生耐药的原因^[17,18],秘鲁和俄罗斯报道MDR-TB和XDR-TB患者中复

治占较高比例^[16,19]。但本研究中有近40.0%的耐二线抗结核药物的MDR-TB和XDR-TB患者无抗结核治疗史,提示在上海市MDR-TB患者中可能存在耐药菌株的传播。已有研究曾对1999—2004年上海市结核病患者进行结核病分子流行病学调查^[20],结果显示绝大多数复治患者是由耐药菌株的近期传播导致。

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