

DOI: 10. 12138/j. issn. 1671-9638. 20233419

· 综述 ·

水解碳青霉烯类 OXA 型 β -内酰胺酶的研究进展

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[摘要] 苯唑西林酶(OXA 酶)属于 D 类 β -内酰胺酶, 因其对苯唑西林具有较高的水解活性而得名。OXA 型 β -内酰胺酶定位于染色体或质粒, 并由质粒、转座子等可移动元件介导其在菌株间的水平转移, 现已衍生出一千余种变体。近年来, 水解碳青霉烯类药物的 OXA 酶出现并在菌株间传播, 给临床抗感染治疗带来巨大挑战。2001 年土耳其从 1 株肺炎克雷伯菌中发现了 OXA-48 酶, 这是在肠杆菌目菌株中第一次发现可水解碳青霉烯类药物的 OXA 酶。随后, 又发现了 OXA-48 酶多种变体, 统称为 OXA-48-like 酶, 其不仅水解青霉素类药物能力强, 还可以水解厄他培南、美罗培南等碳青霉烯类药物, 介导对包括碳青霉烯类在内的多种 β -内酰胺类药物耐药。希瓦氏菌被认为是 *bla*_{OXA-48-like} 基因的起源, 现已报道 12 个起源于希瓦氏菌的 OXA-48-like。为全面掌握可水解碳青霉烯类 OXA 酶的特征和分布, 本文就水解碳青霉烯类药物的 OXA 酶的来源、分布现状、流行特点及发展趋势进行综述。

[关键词] OXA 酶; 碳青霉烯类药物; 水平转移; 希瓦氏菌; β -内酰胺酶

[中图分类号] R363.1⁺4

Advances in carbapenem-hydrolyzing OXA-type β -lactamases

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[Abstract] Oxacillinase (OXA) belongs to class D β -lactamase, named for its high hydrolytic activity on oxacillin. OXA-type β -lactamases locate on chromosomes or plasmids, and their horizontal transfer among strains is mediated by mobile elements such as plasmids and transposons. Over a thousand variants have been derived to date. In recent years, carbapenem-hydrolyzing OXA have emerged and spread among strains, posing a huge challenge to clinical anti-infection treatment. In 2001, OXA-48 was found in a strain of *Klebsiella pneumoniae* in Turkey, which was the firstly reported carbapenem-hydrolyzing OXA in Enterobacterales. Subsequently, various variants of OXA-48 enzyme were identified and nominated as OXA-48-like enzymes. These enzymes not only have strong hydrolytic activity against penicillin, but also hydrolyze carbapenems such as ertapenem and meropenem, mediating resistance to various β -lactam antimicrobial agents, including carbapenems. *Shewanella* spp. is considered to be the origin of the *bla*_{OXA-48-like} gene, and 12 OXA-48-like genes derived from *Shewanella* spp. have been reported. In order to comprehensively understand the characteristics and distribution of carbapenem-hydrolyzing OXA enzymes, this article reviews the origin, distribution status, epidemiological characteristics, and development trends of carbapenem-hydrolyzing OXA.

[Key words] oxacillinase; carbapenems; horizontal transfer; *Shewanella* spp.; β -lactamase

[收稿日期] 2022-09-26

[基金项目] 国家自然科学基金项目(81861138053)

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β -内酰胺酶的产生、进化与传播是革兰阴性菌对 β -内酰胺类药物耐药的最主要机制^[1-2]。根据不同底物谱可将 β -内酰胺酶分为青霉素酶、头孢菌素酶和碳青霉烯酶。碳青霉烯酶是一类能够对碳青霉烯类药物产生水解作用的 β -内酰胺酶,主要包括 Ambler 分子结构分类法中的 A 类、B 类、D 类,其中 A 类酶和 D 类酶利用丝氨酸残基发挥水解作用,按功能分别属于 Bush 分类法中的 2f 和 2d 亚组;而

B 类酶利用金属离子才具有活性,属于 Bush 分类法中第 3 组^[3](见表 1);D 类 β -内酰胺酶有 14 个亚家族,其中 OXA 型种类最为丰富,并不断发现新的变体^[4]。截至 2022 年 9 月,已有 1 144 种 OXA 酶被 β -内酰胺酶数据库 (<http://www.bldb.eu/BLDB.php?prot=D#OXA>)收录,其中水解碳青霉烯类药物的 OXA 型酶数量增加较多,给全球公共卫生带来严重威胁。

表 1 碳青霉烯酶分类及功能特点

Ambler 分子分类	Bush-Jacoby 功能分组	分布情况	活性位点	底物谱水解效率				抑制剂	部分代表酶类
				青霉素类	头孢菌素类	碳青霉烯类	单环 β -内酰胺类		
A	2b、2be、2f	质粒	丝氨酸	++	1st ++ 2nd +/- 3rd/4th +/++	+ / ++	+ / -	克拉维酸、他唑巴坦、舒巴坦	KPC、IMI、TEM、SHV、CTX-M
B	3	染色体、质粒	金属离子 (Zn ²⁺)	++	1st ++ 2nd ++ 3rd/4th ++	+ / ++	-	EDTA	NDM、IMP、VIM
D	2d	染色体、质粒	丝氨酸	++	1st ++ 2nd +/- 3rd/4th +/-	+	-	NaCl、克拉维酸、他唑巴坦	OXA

注: + 表示水解率程度; - 表示未报道相关水解活性。

1 OXA 酶的来源及特点

苯唑西林酶(oxacillinase, OXA 酶)是最早报道的 β -内酰胺酶之一,因其对苯唑西林和氯唑西林的水解率高于青霉素而命名^[5]。早期发现的 OXA 酶仅对青霉素类药物有活性,随着变体的不断出现,其底物谱不断扩大,部分 OXA 酶变体不仅表现出对头孢菌素类抗生素具有水解能力,甚至对碳青霉烯类抗生素也产生一定的水解活性,其活性不受克拉维酸、他唑巴坦、舒巴坦等酶抑制剂的抑制^[6]。

1976 年, Sykes 等^[7]通过基因序列分析首次发现并命名 OXA 酶: OXA-1~OXA-3, 并以其共有的

保守序列作为后续 OXA 酶分类的基础,此后根据发现时间进行数字编号命名 OXA 酶(OXA 酶的种类及分类见表 2)。随着 OXA 酶家族成员的增加, BLDB 数据库将氨基酸同源性高、底物谱相似的酶以首个命名的 OXA 酶的亚家族来命名,称为 OXA-X-like 酶,如 OXA-48-like 酶、OXA-23-like 酶。OXA 酶根据来源不同可分为获得性及内源性两大类, *bla*_{OXA} 基因既可由质粒携带也可由染色体携带^[5]。鲍曼不动杆菌和铜绿假单胞菌中染色体携带 *bla*_{OXA} 基因较多,肺炎克雷伯菌中质粒携带则更为常见。近年来,全球范围内陆续报道了革兰阴性肠杆菌中具有碳青霉烯酶活性的新型 OXA 酶,这显示细菌耐药形势日益严峻。

表 2 OXA 型 β-内酰胺酶种类及来源

亚家族	个数	抗菌谱	Bush-Jacoby 分类	来源	宿主种类	参考网址
OXA-1-like	12	Narrow spectrum ESBLs	2d 2de	A	<i>E. coli</i> ; <i>P. aeruginosa</i> ; <i>K. pneumoniae</i> ; <i>P. mirabilis</i>	http://www. bldb. eu/alignment. php?align = D;OXA-1-like
OXA-2-like	26	Narrow spectrum ESBLs	2d 2de	I, A	<i>P. aeruginosa</i> ; <i>P. mirabilis</i>	http://www. bldb. eu/alignment. php?align = D;OXA-2-like
OXA-10-like	42	Narrow spectrum ESBLs Carbapenemase	2d 2de 2df	I, A	<i>P. aeruginosa</i>	http://www. bldb. eu/alignment. php?align = D;OXA-10-like
OXA-23-like	47	Carbapenemase	2df	I, A	<i>A. baumannii</i> ; <i>A. radioresistens</i> ; <i>K. pneumoniae</i> ; <i>Acinetobacter sp.</i>	http://www. bldb. eu/alignment. php?align = D;OXA-23-like
OXA-24-like	12	Carbapenemase	2df	I, A	<i>A. oleivorans</i> ; <i>Acinetobacter sp.</i>	http://www. bldb. eu/alignment. php?align = D;OXA-24-like
OXA-48-like	46	ESBLs Carbapenemase	2df 2def	I, A	<i>E. cloacae</i> ; <i>E. coli</i> ; <i>P. aeruginosa</i> ; <i>K. pneumoniae</i> ; <i>A. oleivorans</i> ; <i>S. oneidensis</i> ; <i>S. xiamenensis</i> ; <i>S. decolorationis</i> ; <i>Shewanella sp.</i>	http://www. bldb. eu/alignment. php?align = D;OXA-48-like
OXA-50-like	43	Narrow spectrum	2d	I, A	<i>P. aeruginosa</i> ; <i>E. cloacae</i> ; <i>E. coli</i> ; <i>A. oleivorans</i>	http://www. bldb. eu/alignment. php?align = D;OXA-50-like
OXA-51-like	371	Carbapenemase	2df	I, A	<i>A. oleivorans</i> ; <i>A. nosocomialis</i> ; <i>E. cloacae</i> ; <i>E. coli</i> ; <i>K. pneumoniae</i>	http://www. bldb. eu/alignment. php?align = D;OXA-51-like
OXA-55-like	8	Carbapenemase	2df	I	<i>S. algae</i> ; <i>S. chilikensis</i>	http://www. bldb. eu/alignment. php?align = D;OXA-55-like
OXA-58-like	7	Carbapenemase	2df	I, A	<i>A. oleivorans</i> ; <i>E. cloacae</i> ; <i>E. coli</i> ; <i>K. pneumoniae</i>	http://www. bldb. eu/alignment. php?align = D;OXA-58-like
OXA-134-like	30	Carbapenemase	2df	I, A	<i>A. lwoffii</i> ; <i>A. schindleri</i> ; <i>Acinetobacter sp.</i>	http://www. bldb. eu/alignment. php?align = D;OXA-134-like
OXA-143-like	9	Carbapenemase	2df	I, A	<i>A. bereziniae</i>	http://www. bldb. eu/alignment. php?align = D;OXA-143-like
OXA-211-like	17	Carbapenemase	2df	I	<i>A. johnsonii</i>	http://www. bldb. eu/alignment. php?align = D;OXA-211-like
OXA-213-like	81	Carbapenemase	2df	I	<i>A. baumannii</i> ; <i>A. calcoaceticus</i> ; <i>A. lactucae</i> ; <i>A. oleivorans</i> ; <i>A. pittii</i> ; <i>A. schindleri</i> ; <i>Acinetobacter sp.</i>	http://www. bldb. eu/alignment. php?align = D;OXA-213-like
OXA-214-like	7	Carbapenemase	2df	I	<i>A. haemolyticus</i>	http://www. bldb. eu/alignment. php?align = D;OXA-214-like
OXA-229-like	14	Carbapenemase	2df	I	<i>A. bereziniae</i>	http://www. bldb. eu/alignment. php?align = D;OXA-229-like
OXA-286-like	15	Carbapenemase	-	I	<i>Acinetobacter sp.</i>	http://www. bldb. eu/alignment. php?align = D;OXA-286-like
OXA-548-like	6	-	-	I	<i>S. baltica</i> ; <i>S. hafniensis</i>	http://www. bldb. eu/alignment. php?align = D;OXA-548-like
OXA-664-like		Carbapenemase	-	I	<i>Acinetobacter sp.</i> ; <i>A. tandoii</i>	http://www. bldb. eu/alignment. php?align = D;OXA-664-like
OXA-679-like	6	Carbapenemase	-	I	<i>A. calcoaceticus</i> ; <i>A. lactucae</i> ; <i>A. pittii</i>	http://www. bldb. eu/alignment. php?align = D;OXA-679-like

注:来源参考 β-内酰胺酶数据库([http://www. bldb. eu/](http://www.bldb.eu/)); - 表示尚未给出明确分类;“来源”数据列中的 A 为获得性(acquired),I 为内源性(intrinsic);ESBLs 为超广谱 β-内酰胺酶。

2 OXA 酶的流行分布

目前,OXA 酶宿主菌范围不断扩大,从最初发现的鲍曼不动杆菌、铜绿假单胞菌,到目前发现的肺炎克雷伯菌、大肠埃希菌、阴沟肠杆菌以及其他肠杆菌^[8-10]。

不动杆菌中几乎所有 OXA 酶都具有碳青霉烯酶活性,联合外排泵过表达机制可介导对碳青霉烯类抗生素高水平耐药。中东和北非等地区耐碳青霉烯类鲍曼不动杆菌(CRAB)分离率超过 70%^[11]。鲍曼不动杆菌携带染色体固有 OXA-51-like 酶,该家族已发现 363 个变种,是造成鲍曼不动杆菌耐药的首要因素。OXA-23 是鲍曼不动杆菌中常见的获得性 OXA 酶,最初在苏格兰发现的 CRAB 菌株中分离并命名,现已报道发现 44 个变体,主要在欧美地区流行^[12-14]。OXA-24/40 首次在西班牙分离出的 CRAB 中发现,此后陆续衍生出 11 个变体,在中国、美国、埃及、土耳其及伊朗等国家均有流行^[15-17]。2003 年在法国图卢兹发现的 1 株 CRAB 中检测出 OXA-58,其与其他 OXA 家族同源性低,被列为 OXA 新的亚家族,该家族现已衍生出 7 个变种,主要通过质粒传播,在欧洲、亚洲及拉美地区引起医院感染暴发^[18-20]。

OXA-48-like 酶由于主要在肠杆菌目细菌中传播而备受关注。自 2001 年在土耳其伊斯坦布尔分离的肺炎克雷伯菌中首次检出水解碳青霉烯类活性的 OXA-48 以来,其变体在欧洲、亚洲、北非、中东地区的肠杆菌目细菌中广泛传播^[21-22]。截至 2022 年 6 月,世界范围内已确认和命名 45 个 OXA-48-like 酶。我国主要以 OXA-181 及 OXA-232 两大变体为主,两者仅存在 1 个氨基酸差异。自印度 1 株肺炎克雷伯菌分离出 OXA-181 后,在其他肠杆菌中也被分离出来,呈现出世界范围内流行的态势^[23-25]。2013 年,法国 1 株肺炎克雷伯菌中首次检出 OXA-232,而后在我国江浙沪地区相继检出,主要通过质粒进行菌株间水平转移^[26-28]。OXA-50-like 酶为假单胞菌所特有,现已衍生出 43 个变体,其与外排泵过表达、外膜蛋白减少或丢失等机制共同作用,是造成假单胞菌多重耐药的重要原因^[29]。Nitz 等^[30]首次临床分离的铜绿假单胞菌中检测出 OXA-23 和 OXA-51,该菌株存在高水平多重耐药。变形杆菌具有携带多种类型水解碳青霉烯类 OXA 酶的特征。Bonnin 等^[31]发现 OXA-23、OXA-24 及 OXA-58 在法

国和比利时地区分离的变形杆菌中流行。我国也在奇异变形杆菌中检出了 *bla*_{OXA-23} 和 *bla*_{OXA-48} 基因^[32]。

转座子、整合子等可移动元件介导的耐药基因的水平转移是导致耐药基因在不同种属之间传播的重要机制^[33]。此外,插入元件中的调控序列能够促进基因的过表达,例如鲍曼不动杆菌中常见的插入序列 ISAba1,隶属于 IS4 家族,能够提供强启动子以增强其下游 *bla*_{OXA-23}、*bla*_{OXA-27} 等基因的表达,也可形成转座子介导 *bla*_{OXA} 基因的转移。接合型质粒携带的基因可随质粒转移,更易造成耐药性的传播^[34]。

3 OXA 酶功能研究

不同 OXA 酶具有不同的底物谱,Bush-Jacoby 分类法^[35]根据酶的功能和表型,将 OXA 酶分为 2d、2de、2df 和 2def 四个功能组。OXA 酶对氯唑西林或苯唑西林水解活性高于对青霉素的 50%,则被归为 2d 功能组,其中大部分属于窄谱酶(OXA-1-like 酶、OXA-50-like 酶),其仅对青霉素类药物有明显的水解活性,对头孢菌素类抗生素作用微弱,且活性不会被克拉维酸抑制。近年来,部分窄谱酶因单一或多个氨基酸位点突变而发生底物谱变化,使得某些 OXA 酶具有广谱性质,被归为 2de 亚组 ES-BLs,主要为 OXA-2-like 酶及 OXA-10-like 酶。土耳其分离的 1 株铜绿假单胞菌中发现的 OXA-15 是由 OXA-2 发生单一氨基酸突变形成的超广谱 OXA 酶,对头孢他啶有较高的水解活性。OXA-10-like 酶中具有广谱水解活性的变体较多。与 OXA-10 相比,OXA-11 有两个氨基酸差异,增加了其对三代头孢的水解能力。OXA-145 是 OXA-10 的另一个变体,第 165 位氨基酸的缺失扩大该酶家族的底物谱,减弱了对青霉素类药物的水解活性。Bonnin 等^[36]在法国 1 株铜绿假单胞菌中检出 OXA-198,被归为一个新的 D 类酶亚组,*bla*_{OXA-198} 位于 IncP 型质粒携带的 I 类整合子上,显著降低对碳青霉烯类抗生素的敏感性。Kotsakis 等^[37]在医院污水分离的肠杆菌中发现同样定位于 I 类整合子上的 *bla*_{OXA-655} 和 *bla*_{OXA-656},均为 OXA-10 的新变体,这些变体具有更强的碳青霉烯类水解能力,存在水平传播的风险。

目前,关注较多的是由于活性位点变化而产生碳青霉烯类水解能力的 2df 亚组 OXA 酶。OXA-23 是第一个被确认水解碳青霉烯类的 OXA 酶,其对亚胺培南的水解活性显著提高,而对广谱头孢菌素类抗生素及氨曲南水解能力弱^[38]。与 OXA-23

相比, OXA-27 有两个氨基酸差异, 同样表现出对碳青霉烯类抗生素的水解活性。此外, 我国报道了单个氨基酸突变产生的新变种 OXA-423, 同样具有碳青霉烯类抗生素的水解活性, 但对克拉维酸、他唑巴坦等酶抑制剂敏感^[39]。*bla*_{OXA-51} 基因编码一种弱的碳青霉烯酶, 多为内源性携带, 也可由质粒携带, 质粒相邻的 ISAbal 可促使该基因过表达, 表现出对碳青霉烯类药物的高水平耐药^[40]。OXA-58 由质粒携带, 对青霉素类和碳青霉烯类抗生素水解活性较弱, 而对广谱头孢菌素类抗生素活性较差, 多个 ISs 协同转座可能是其传播的重要方式^[41]。

肠杆菌中最常见的碳青霉烯酶为 OXA-48, IS1999 及多种质粒的高效转移加速了 *bla*_{OXA-48} 基因在细菌间的水平传播^[42]。OXA-181 是分布最为广泛的 OXA-48-like 酶家族成员, 其与 OXA-48 有四个氨基酸差异, 且表现出极为相似的水解特征。Aertker 等^[43]证明单一氨基酸替换能够使 OXA-48-like 酶对碳青霉烯类抗生素表现出不同的水解活性。OXA-162 与 OXA-48 仅有一个氨基酸差异, 同样能够介导肠杆菌对碳青霉烯类抗生素耐药。Sommer 等^[44]在大肠埃希菌中发现质粒携带的 *bla*_{OXA-484} 基因, OXA-484 与 OXA-181 存在 1 个氨基酸替换, 其对碳青霉烯类抗生素的水解能力略低于 OXA-48 及 OXA-181。比利时分离出的 1 株肺炎克雷伯菌中发现了 OXA-519, 其与 OXA-48 有 1 个氨基酸差异, 表现出对哌拉西林/他唑巴坦耐药和对亚胺培南敏感性降低^[45]。然而, 并不是所有的 OXA-48 变体都对碳青霉烯类抗生素有水解活性。OXA-405 与 OXA-48 具有相似的主体结构, *bla*_{OXA-405} 位于转座子 Tn1999 上, IS1R 插入替代了保守序列缺失的 4 个氨基酸, 使得 OXA-405 对碳青霉烯类几乎完全失去水解活性, 仅表现出 ESBL 活性^[46]。Poirel 等^[47]在肠杆菌中发现 OXA-163, 与 OXA-48 相比有 5 个氨基酸变化, 能够水解青霉素类、第三代头孢菌素类以及碳青霉烯类抗生素, 被分类为兼具头孢菌素类和碳青霉烯类抗生素水解活性的 2def 亚组。Gomez 等^[48]从阿根廷 1 例白血病患者体内分离出携带 OXA-163 的肺炎克雷伯菌, 治疗后又在其体内分离出携带 OXA-247 的肺炎克雷伯菌, OXA-247 是 OXA-163 的新变体, 两者有相似的底物谱, 但对广谱头孢菌素类抗生素的水解活性减弱。

20 世纪 70 年代 β -内酰胺酶抑制剂应用于临床, 常见的酶抑制剂包括克拉维酸、他唑巴坦和舒巴坦等, 能够对 OXA 酶产生不同程度的抑制作用, 他

唑巴坦对 OXA-1 仅表现弱抑制作用; 对于同一家族成员, 他唑巴坦对 OXA-32 表现强抑制作用, 克拉维酸则相对较弱, 而 OXA-53 对后者更加敏感^[49]。研究^[50-51]显示, 头孢他啶/阿维巴坦、亚胺培南/西司他丁等新型酶抑制剂复合制剂对某些产 D 类酶的肠杆菌有一定杀灭作用。

4 OXA 酶与希瓦氏菌的关系研究

希瓦氏菌是一种水体环境生存的革兰阴性菌, 早期认为该类菌仅存在于腐败变质的高蛋白水产食品中。近年研究^[52-53]显示, 希瓦氏菌的部分种属与人类感染密切相关, 易感人群可通过接触或食用含有希瓦氏菌的水、海产、食品等引起腹泻、溶血性反应以及软组织感染等疾病。临床常见的希瓦氏菌包括厦门希瓦氏菌、海藻希瓦氏菌和腐败希瓦氏菌。

希瓦氏菌染色体固有携带 *bla*_{OXA-48-like} 基因, 在报道的 OXA-48-like 酶中有 26 个与希瓦氏菌固有携带的 OXA 高度同源, 说明希瓦氏菌属可能是 OXA-48-like 酶的起源, 并在 *bla*_{OXA-48} 基因的传播中发挥重要作用^[54]。Poirel 等^[55]首次在奥奈达湖希瓦氏菌中发现染色体定位的 *bla*_{OXA-54} 基因, OXA-54 与 OXA-48 同源率为 92%, 可以显著水解苯唑西林, 常见的酶抑制剂仅对其有弱抑制作用。厦门希瓦氏菌与奥奈达湖希瓦氏菌亲缘关系接近, 分离自我国福建厦门近海沉积物中。Dabos 等^[56]和 Jousset 等^[57]在厦门希瓦氏菌中报道了染色体固有携带 *bla*_{OXA-535}, OXA-535 与 OXA-48 同源率为 91.3%, 对多种 β -内酰胺类药物有高效水解作用。在沼泽植物^[54]、河水^[58-59]、淡水^[60]、养殖场废水^[61-62]以及医院污水^[63-64]等环境来源的厦门希瓦氏菌中不断检出 OXA-48-like 酶相关基因。因此, 希瓦氏菌被认为是自然环境中耐药基因的重要载体和储存库, 通过转座子介导耐药基因快速转移和传播, 对人类及动物的健康造成潜在威胁。

5 总结与展望

OXA 酶是革兰阴性菌中种类繁多、分布广泛的一类 β -内酰胺酶, 可由质粒、转座子等多种可移动元件携带并转移, 实现 OXA 酶在不同菌株间的快速传播。近年来, 可以水解碳青霉烯类抗生素的 OXA 酶新变体不断出现, 并在人群、动物及环境中传播, 对公共卫生造成潜在的、巨大的威胁^[10]。意大利、

西班牙等南欧国家产 OXA-48-like 酶耐碳青霉烯类肠杆菌 (carbapenem-resistant Enterobacterales, CRE) 占比超过产 KPC、NDM 等碳青霉烯酶 CRE, 是 CRE 的主要耐药机制^[65]。在我国, 尽管具有碳青霉烯类药物水解功能的 OXA 酶在 CRE 中占比较低, 但不断有 OXA-181、OXA-232、OXA-427、OXA-484、OXA-546、OXA-894 和 OXA-913 等新的具有碳青霉烯类药物水解活性的亚型被检出, 提示需高度关注 OXA 酶的流行和进化。环境、动物及人群中 *bla*_{OXA} 的检测、OXA 酶功能研究和持续监测, 对掌握 OXA 酶的分布特征和流行趋势, 保障食品安全, 减慢或抑制耐药基因在菌株间的传播和扩散, 最大限度减少耐药菌的危害具有重要意义。

利益冲突: 所有作者均声明不存在利益冲突。

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(本文编辑:孟秀娟、陈玉华)

本文引用格式:姜雪琪,李娟. 水解碳青霉烯类 OXA 型 β -内酰胺酶的研究进展[J]. 中国感染控制杂志, 2023, 22(9): 1121 - 1128. DOI: 10. 12138/j. issn. 1671 - 9638. 20233419.

Cite this article as: JIANG Xue-qi, LI Juan. Advances in carbapenem-hydrolyzing OXA-type β -lactamases [J]. Chin J Infect Control, 2023, 22(9): 1121 - 1128. DOI: 10. 12138/j. issn. 1671 - 9638. 20233419.