鲍曼不动杆菌的耐药机制研究进展

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摘要：多重耐药鲍曼不动杆菌是一种院内感染病原体，重症患者感染概率大，严重威胁着患者的生命安全。本文就多重耐药的鲍曼不动杆菌的临床流行现状及其对不同抗生素耐药机制的研究进展进行综述。

关键词：鲍曼不动杆菌；多重耐药；感染
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Research advances in resistance mechanism of Acinetobacter baumannii

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Abstract: As a kind of nosocomial pathogen spreading throughout the world, the multidrug- resistant(MDR) Acinetobacter baumannii threatens patient's life so much that the prevention and treatment are challenging for clinicians. This review will summarize the clinical epidemiology and the mechanism of MDR Acinetobacter baumannii's resistancy in recent studies.
Keywords: Acinetobacter baumannii; multidrug-resistant; infection

当前临床上出现了越来越多的多重耐药细菌，严重威胁着患者的生命，带来沉重的经济负担，但相应的抗菌药物的发展却进展缓慢[1-2]。其中屎肠球菌、金黄色葡萄球菌、肺炎克雷伯菌、鲍曼不动杆菌、铜绿假单胞菌和大肠埃希菌是在全世界流行且耐药性最为突出的细菌[2-4]。在世界各地，由鲍曼不动杆菌引起的感染在不断增加[5-6]。为有效治疗多重耐药菌感染并遏制多重耐药菌的传播，临床上对多重耐药菌耐药机制的研究越来越多，对多重耐药菌鲍曼不动杆菌的研究也在兴起。

1　多重耐药的鲍曼不动杆菌感染的临床现状

重症患者感染鲍曼不动杆菌的风险很高，导致包括呼吸机相关性肺炎、菌血症、皮肤及软组织感染、心内膜炎、泌尿系感染和脑膜炎等[6-7]。感染鲍曼不动杆菌后患者的死亡率为35%甚至更高[4,8]。碳青霉烯类耐药鲍曼不动杆菌已经成为最受关注的院内感染病原菌[9]。有研究显示，从ICU分离的鲍曼不动菌株超过50%为碳青霉烯类耐药菌株，全球卫生系统每年用于治疗的费用约7.42亿美元[10]。目前发现的鲍曼不动杆菌有20余种，临床最为常见的A.鲍曼不动杆菌[11]、鲍曼不动杆菌(基因种13TU)、不动杆菌pittii(基因种3)与院内获得性感染密切相关[12]。与之相比如乙酸钙不动杆菌与临床感染的关系就小得多。这4种菌在生物学上很难进行区分，在临床上常被认为是鲍曼不动杆菌复合体。有调查显示，57.6%的鲍曼不动杆菌菌株来自呼吸道，23.9%来自血行感染，9.1%来自皮肤或伤口感染[13]。调查显示鲍曼不动杆菌是第5大导致呼吸机相关性肺炎的病原体(6.6%)，是导致血行感染的第13位病原菌[14]。越来越多对于鲍曼不动杆菌基因序列的研究加深了我们对细菌基因构成的认识[7]。在哺乳动物和无脊椎动物的感染模型中细菌突变研究已经为我们提供了一些关于不动杆菌发病机制有价值的见解。与疾病有关的细菌毒力因素包括膜表面结构和脂多糖的酶，如磷脂酶D、铁采集系统和调节蛋白。许多研究已经确定了细菌的毒力因子，包括细菌的细胞外基质、生物膜形成、泵外排机制[8]。

2　鲍曼不动杆菌对多种抗生素的耐药机制

2.1　头孢菌素　大多数鲍曼不动杆菌都对头孢菌素耐药，包括三代头孢(如头孢他啶)和四代头孢(如头孢吡肟)。其他革兰阴性菌的β-内酰胺酶可以被诱导产生或者永久抑制，而鲍曼不动杆菌产生的β-内酰胺酶被并非由诱导产生[9-10]。有研究证实当某种上游基因(如ISAba125)插入，增强启动子活性后，鲍曼不动杆菌表达的β-内酰胺酶增加，这与临床耐药性有关[11]。鲍曼不动杆菌也能产生超广谱β内酰胺酶导致对头孢菌素耐药[12]。

2.2　碳青霉烯　对碳青霉烯耐药的鲍曼不动杆菌已经成为一种重要的院内感染病原体[13]。对碳青霉烯类抗生素的耐药是由于鲍曼不动杆菌能先天或后天产生碳青霉烯酶。鲍曼不动杆菌通过染色体编码OXA-5基团表达低水平的碳青霉烯酶，通过插入序列获得增强启动子，与β-内酰胺酶类似，使得碳青霉烯的最小抑菌浓度升高[14-15]。当鲍曼

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不动杆菌的质粒获得了某种OXA基团，β－内酰胺酶基因也会对碳青霉烯产生耐药。有研究显示有5个主要的OXA基团与碳青霉烯耐药有关，分别为OXA-23、OXA-40、OXA-58、OXA-143和OXA-235[16-17]。有研究表明由国际克隆菌株2携带的OXA-23基团目前最为流行[18-19]，而OXA-51、OXA-23在ICU环境中最为流行[20]。也有报道发现鲍曼不动杆菌携带的OXA-164基团突变为OXA-58，并且证实该耐药性是由于抗生素的使用逐步获得的[21]。近来有研究发现无OXA基团的鲍曼不动杆菌能从大肠埃希菌获得对碳青霉烯的耐药性，如新德里金属β－内酰胺酶NDM-1。从2011年起，各国研究发现耐碳青霉烯的鲍曼不动杆菌会产生NDM-1[22-23]。鲍曼不动杆菌获得的其他类型的金属β－内酰胺酶也有报道[24-27]。有报道波多黎各发现KPC基团的碳青霉烯酶，但没有证据显示有更大范围的传播[28]。

2.3 舒巴坦 舒巴坦是一种β－内酰胺酶抑制剂，常与氨苄西林或头孢哌酮一起使用以减轻A型β－内酰胺酶的水解作用，也具有包括对抗鲍曼不动杆菌在内的不动杆菌属的自身活性，推测与青霉素结合蛋白(penicillin-binding proteins，PBPs)有关[29-30]。鲍曼不动杆菌来源的头孢菌素酶(acinetobacter-derived cephalosporinase，ADC)与对舒巴坦的耐药有关[31]。也有报道称PBPs的表达以及TEM-1β－内酰胺酶的产生均与鲍曼不动杆菌对舒巴坦耐药有关[32-33]。

2.4 利福平 利福平发挥作用的原理是结合细菌RNA聚合酶并抑制转录。对利福平耐药的主要机制是β亚基的氨基酸置换[34]。由于编码该亚基的rpoB基因可能发生突变，单一的利福平治疗在任何抗菌治疗中都是不适用的，当然也包括鲍曼不动杆菌。除此机制外对利福平的酶改修饰以及外排机制也与对其耐药有关[34-35]。

2.5 氨基糖苷 氨基糖苷类与30S核糖体亚基的16S核糖体RNA结合抑制蛋白质合成。鲍曼不动杆菌分泌各种糖苷类修饰酶获得氨基糖苷类耐药性[36-38]。另一个氨基糖苷耐药的机制是16S核糖体RNA转移酶的产生，特别是ArmA。ArmA使与氨基糖苷结合的16S核糖体鸟嘌呤残端甲基化，以保护其不与氨基糖胺类结合[39]。产ArmA的鲍曼不动杆菌与耐药高度相关，这通常在国际克隆株2见到[40-41]。

2.6 喹诺酮 氟喹诺酮与DNA回旋酶和拓扑异构酶Ⅳ结合干扰DNA合成导致细胞死亡。对氟喹诺酮耐药的基本机制是编码目标蛋白的基因在喹诺酮耐药的决定区发生氨基酸替换[41]。这一机制导致了对高浓度喹诺酮的耐药。另外，鲍曼不动杆菌可能过表达外排泵来获得中度的喹诺酮耐药[42]。

2.7 多黏菌素 多黏菌素是一种阳离子抗菌肽，能够通过结合脂质A启动其抗菌活性。多黏菌素的耐药机制因菌株不同而有所差异。Girardello等[43]的研究显示，对多黏菌素敏感的菌株经过对多黏菌素的暴露后出现对多黏菌素的耐药改变，实验证实出现了pmrB的突变以及ISAba125插入序列干扰基因lpxA的表达。鲍曼不动杆菌在双组分系统中发生的突变主要表现在pmrAB基因的突变[44]，导致了反应调节子PmrA和感应蛋白激酶PmrB的过表达，这也说明PmrAB调节家族发挥着对多黏菌素的抗性作用，目前还没有对鲍曼不动杆菌中的PmrAB调节单元进行更详细的研究。在对其他细菌的研究中发现pmrAB基因的突变也与脂多糖的修饰有关。PmrB水平的变化与磷酸乙醇胺对脂质A的修饰有关[45-46]。脂质A的完全缺失会导致对多黏菌素的耐药，但PmrAB是否直接在此过程中发挥作用有待进一步研究，此现象也仅见于实验室分离菌株而非临床分离的菌株[45]。

2.8 四环素 四环素通过与30S核糖体亚基结合发挥活性。细菌通过外排泵的活化或者产生Tet蛋白与70S核糖体结合产生耐药作用。四环素能够阻止这种机制，但是仍会被鲍曼不动杆菌Ade型的外排泵排出，特别是当这些外排泵过表达时[47]。鲍曼不动杆菌对新一代四环素药物替加环素的耐药性与adeRS控制的RND型外排泵AdeABC有关[48]。临床分离株中adeRS基因序列的多样性决定了对替加环素耐药的程度有差异[49]。其他基因如在大肠埃希菌中的BaeSR基因控制其外排泵，这也提示在鲍曼不动杆菌中可能存在相似的机制。实际上删除BaeSR基因会导致外排泵AdeABC、AdeIJK和MacAB-TolC的显著减少，导致了对替加环素的敏感性增加[50]。

3 sRNA与鲍曼不动杆菌耐药

sRNA(smallRNA)在细菌中能对各种细胞进程进行调节。在大肠埃希菌和沙门菌中非编码RNA的调节的表达模式和调节机制已经有相关研究。有研究对鲍曼不动杆菌菌株ATCC17978进行了分析，找到31个候选sRNA，对菌株ATCC15308通过Northern印记确定了3个sRNA[51]。在多重耐药鲍曼不动杆菌菌株AB5075中，使用RNA测序鉴定了78个sRNA[52]。

在肠杆菌中，RNA结合蛋白Hfq的一个功能是促进sRNA及其同源mRNA的相互作用[53]。在不动杆菌的近亲铜绿假单胞菌中，Hfq在sRNA调节机制中发挥的作用与肠杆菌的调节模式不同[54-55]。在不动杆菌属中，仅有在无毒力的baylyi不动杆菌对Hfq的相关研究。Hfq具有异常长的，富含甘氨酸的C末端，这是不动杆菌属的独特特征，这可能影响sRNA结合Hfq的部位以及如何与Hfq结合，以及Hfq如何影响其他细胞因子[56]。在其他病原体中，RNA结合蛋白如CsrA的缺失通常导致无毒表型[57]，然而Hfq在鲍曼不动杆菌毒力或耐药性中的机制仍需进一步研究。对Baylyi不动杆菌中的sRNA Aar的调节作用的研究结果在鲍曼不动杆菌中也是适用的[52,58]。有在其他革兰阴性菌中的研究表明Hfq具有铁稳态的作用，sRNA介导的基因调节可能与铁稳态有关，有蛋白质组研究显示鲍曼不动杆菌Hfq蛋白水平在限铁环境下降低[59]。Hfq蛋白和Hfq依赖的sRNA已被证实在鲍曼不动杆菌的耐药性中发挥作用，sRNA能够控制许多抗生素作用靶点的表达[60-61]。在肠杆菌中，主要膜孔蛋白OmpA、OmpC、OmpD和OmpF由几种sRNA协同控制。由于OmpA膜孔蛋白在鲍曼不动杆菌毒力和耐药性中的重要作用[62]，需要进一步研究是否存在其他类似由sRNA介导的膜孔蛋白OmpA或其他膜蛋白的调节[63]。特别是在发生感染和暴露于抗生素环境中，需要进一步阐明sRNA的调节机制以及鲍曼不动杆菌中的RNA结

合蛋白的分类和特性。

4 结语

随着时间推移，鲍曼不动杆菌对多种抗生素都产生了耐药性。在过去的20多年，由于鲍曼不动杆菌不断累积的耐药能力，使其成为最为受关注的一种医院获得性病原体。目前基因工具在多重耐药菌研究中的应用越来越普遍，越来越多关于鲍曼不动杆菌基因序列、动物感染模型以及细菌突变的研究为鲍曼不动杆菌的致病及耐药机制提供了有价值的见解。

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