·综 述·

头孢地尔：新型铁载体头孢菌素抗多重耐药革兰阴性杆菌感染

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摘 要：抗菌药物耐药是目前全世界面临的重要公共卫生问题之一，亟需开发有效的广谱抗菌药物以应对多重耐药革兰阴性杆菌的感染。头孢地尔是日本 Shionogi 公司开发的新型铁载体头孢菌素类抗菌药物。该药物对碳青霉烯耐药的肠杆菌目细菌 (carbapenem resistant Enterobacterales, CRE)、铜绿假单胞菌、鲍曼不动杆菌和嗜麦芽窄食单胞菌等具有广谱强效的抗菌活性。该药物克服了革兰阴性杆菌因外膜孔道蛋白表达量下调和主动外排泵表达量上调产生的耐药性，并对丝氨酸酶和金属碳青霉烯酶具有较好的稳定性。该药可用于治疗由革兰阴性杆菌引起的复杂性尿路感染 (包括肾盂肾炎)、院内获得性肺炎和呼吸机相关性肺炎。文中通过汇总头孢地尔的化学结构、抗菌作用机制、体外抗菌活性、药代动力学、药效学和临床治疗等信息，展现头孢地尔作为新型铁载体头孢菌素在治疗多重耐药革兰阴性杆菌感染中的应用前景。

关键词：头孢地尔；铁载体头孢菌素；药代动力学；药效学；体外抗菌活性

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Cefiderocol: a novel siderophore cephalosporin against multi-drug resistant Gram-negative bacilli infections

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Abstract: Antimicrobial resistance is one of the critical public health issues in the world. There is an urgent need to develop effective broad-spectrum antibiotics to treat the infection of multi-drug resistant Gram-negative bacilli. Cefiderocol, developed by the Shionogi Inc. in Japan, is a new type of iron carrier cephalosporin antibiotics, which overcomes the drug resistance of Gram-negative bacilli due to the down-regulation of outer membrane pore protein and the up-regulation of efflux pump, and has good stability to serine- and metallo-carbapenemases. This drug has a broad spectrum and strong antibacterial activity against carbapenem-resistant Enterobacteriaceae (CRE), *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*. Cefiderocol can be used to treat complex urinary tract infections (including pyelonephritis), hospital-acquired pneumonia, and ventilator-associated pneumonia. By summarizing the chemical structure, antibacterial mechanism, *in vitro* antibacterial activity, pharmacokinetics, pharmacodynamics, and clinical treatment of cefiderocol, this review shows the application potential of cefiderocol as a new iron carrier cephalosporin in the treatment of multi-drug resistant Gram-negative bacilli infections.

Keywords: cefiderocol; siderophore cephalosporin; pharmacokinetics; pharmacodynamics; *in vitro* antibacterial activity

抗菌药物耐药是全世界面临的重要公共卫生问题之一。碳青霉烯耐药的肠杆菌目细菌 (carbapenem-resistant Enterobacterales, CRE) 的分离率呈逐年上升趋势，碳青霉烯耐药的鲍曼不动杆菌 (carbapenem-resistant *Acinetobacter baumannii*, CRAB) 的分离率稳居不下，已引发全球高度关注。世界卫生组织预测，2050 年因抗菌药物耐药将造成每年 1 000 万人死亡，全球累积经济损失可达 100 万亿美元[1]。2019 年美国疾病预防控制中心将 CRAB 和 CRE 列为紧急威胁，多重耐药铜绿假单胞菌列为严重威胁[2]。这些多重耐药菌几乎对所有可用的抗菌药物都耐药，使临床抗感染治疗陷入困境[3]。因此，迫切需要开发有效的广谱抗菌药物以应对多重耐药革兰阴性杆菌导致的感染。

头孢地尔 (cefiderocol, S-649266)，是日本 Shionogi 公司开发的新型铁载体头孢菌素类抗菌药物 (商品名为 Fetroja)。该药物以氯邻苯二酚结构与 Fe^{3+}形成头孢地尔-Fe^{3+}螯合复合物，通过铁转运蛋白穿透革兰阴性杆菌的细胞外膜，转运至细菌的周浆间隙[4]。头孢地尔在周浆间隙富集，通过作用于青霉素结合蛋白 3 (penicillin binding protein 3, PBP3) 对 CRE、CRAB、多重耐药铜绿假单胞菌和嗜麦芽窄食单胞菌等具有较好的体外抗菌活性[4]。该药已于 2019 年 11 月在美国上市，可用于治疗由革兰阴性杆菌引起的复杂性尿路感染和院内获得性细菌性肺炎/呼吸机相关细菌性肺炎[4]。

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本文对头孢地尔的化学结构、抗菌作用机制、体外抗菌活性、药代动力学、药效学和临床治疗等方面的相关信息进行总结，头孢地尔可作为新型铁载体头孢菌素在治疗革兰阴性杆菌感染，尤其是多重耐药革兰阴性杆菌感染中具有较好的应用前景。

1 头孢地尔的化学结构式及其作用机制

头孢地尔是新型铁载体头孢菌素，由头孢菌素母核 (7-氨基头孢烷酸)、C3 侧链和 C7 侧链组成。头孢菌素母核部分存在 PBP3 的结合位点[5]。C3 侧链与头孢吡肟相似，连接的吡咯烷鎓离子基团 (环季铵盐) 提高了头孢地尔对 β 内酰胺酶的稳定性。C7 侧链与头孢他啶相似，羧基基团的引入改善了头孢地尔对外膜的渗透性，氨基噻唑基团、肟和二甲基基团提高了头孢地尔的抗菌活性[5]。

头孢地尔通过 C3 侧链上的氯邻苯二酚基团螯合铁离子 (Fe^{3+})，形成的复合物可被革兰阴性杆菌外膜铁转运蛋白结合，并被转运至细菌周浆间隙，富集达到更高的浓度，该过程由 TonB-ExbB-ExbD 复合体提供能量[6] (图 1)。头孢地尔在周浆间隙中通过头孢菌素母核作用于

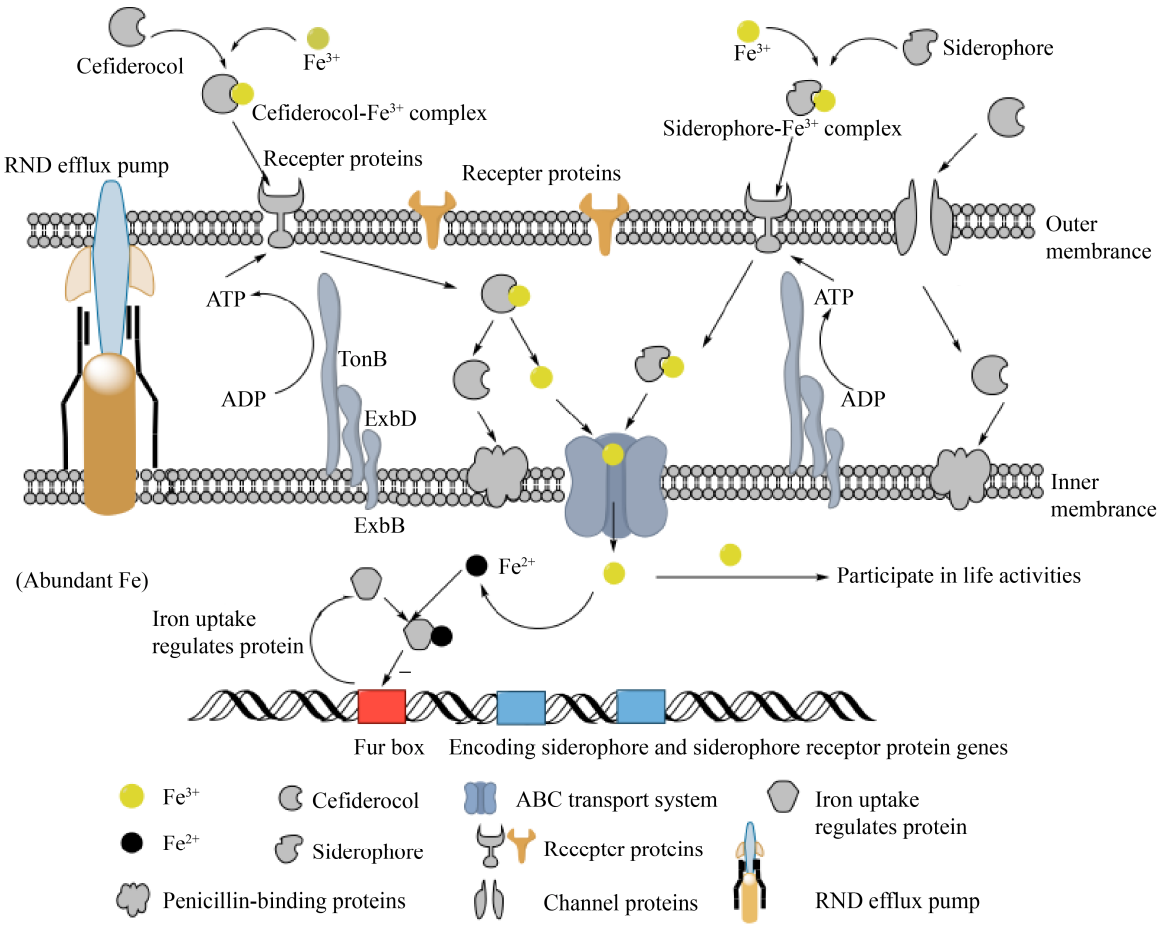

图 1 头孢地尔进入革兰阴性杆菌内的分子机制

Figure 1 Molecular mechanism of cefiderocol entry into Gram-negative bacilli.

PBP3 发挥抗菌活性，抑制肽聚糖的合成，进而导致细菌的死亡[7]。革兰阴性杆菌可分泌铁载体，以备在细胞外铁浓度较低时可从环境中摄取利用铁离子[6]。铁载体转运蛋白表达受 Fur 蛋白-Fe^{2+} 复合物调控。乏铁环境下，Fur 蛋白-Fe^{2+}复合物解离，解除对 Fur 盒的抑制，铁载体通道蛋白表达量上调，有利于头孢地尔发挥抗菌活性[6]。

2 头孢地尔的体外抗菌活性

2.1 革兰阴性杆菌及多重耐药革兰阴性杆菌

2.1.1 体外抗菌活性

肠杆菌目细菌、鲍曼不动杆菌、铜绿假单胞菌和嗜麦芽窄食单胞菌等革兰阴性杆菌对头孢地尔具有较好的体外敏感性[8]，详见表 1。目前头孢地尔临床耐药株的分离率较低。一项北美洲和欧洲 13 个国家监测碳青霉烯不敏感的革兰阴性杆菌对头孢地尔体外敏感性研究中发现，仅 2.3% (29/1 272) 的菌株头孢地尔的最低抑菌浓度 (minimal inhibitory concentration, MIC)≥8 μg/mL[9]。

头孢地尔对多种 β-内酰胺酶，包括 A 类超广谱 β 内酰胺酶 (extended β-lactamases，ESBLs，CTX-M 型酶或 SHV 型酶)、丝氨酸碳青霉烯酶 (如 KPC、NMC 和 SME 酶)、B 类金属碳青霉烯酶 (如 NDM、VIM、IMP 和 L1 酶) 和 D 类碳青霉烯酶 (如 OXA-48 酶、OXA-23/24/40 酶) 均具有较好的稳定性[8,10-12]。对于携带 C 类 β 内酰胺酶如染色体 AmpC 酶的铜绿假单胞菌或阴沟肠杆菌，头孢地尔是该类酶的低亲和力底物和酶过量表达的弱诱导剂。因此，头孢地尔对携带该类酶的菌株具有较好的体外抗菌活性[13]。革兰阴性杆菌外膜孔道蛋白的缺失或主动外排泵基因过表达可导致菌株对 β 内酰胺类药物耐药[14]。而通过实验室构建肺炎克雷伯菌 *ompK35/36* 基因敲除株和铜绿假单胞菌主动外排泵 MexAB-OprM 系统过表达时发现，头孢地尔的 MIC 值较亲体株虽略有增加 (增加 2–4 倍)，但仍对头孢地尔保持敏感[8]。

表 1 头孢地尔对革兰阴性杆菌的体外抗菌活性

Table 1 The *in vitro* antimicrobial activity of cefiderocol against Gram-negative bacilli

Organisms	Total[a]	MIC_{50} range (μg/mL)	MIC_{90} range (μg/mL)	References
Enterobacterales				
Klebsiella pneumoniae	5 164	≤0.03–1.00	0.12–4.00	[10,14-21]
Klebsiella oxytoca	939	≤0.03–0.25	0.25–1.00	[16-17,19-20]
Escherichia coli	5 609	≤0.06–1.00	0.25–4.00	[10,15-20]
Serratia marcescens	1 862	≤0.03–0.50	≤0.06–2.00	[10,16-17,19-20]
Serratia liquefaciens	33	0.06	0.12	[17]
Proteus mirabilis	14	≤0.03	0.25	[22]
Enterobacter cloacae	1 246	0.12–0.50	1.00	[10,16-17,20-21]
Providencia stuartii	11	0.25	0.50	[21]
Citrobacter freundii	655	≤0.06–0.12	0.12–1.00	[10,16-17]
Nonfermentative bacilli				
Pseudomonas aeruginosa	4 012	0.06–0.50	0.50–2.00	[15-21,23]
Acinetobacter baumannii	2 864	0.06–0.50	0.12–8.00	[14-21,23]
Acinetobacter pittii	111	0.12	0.50	[16]
Stenotrophomonas maltophilia	1 142	0.06–0.25	0.25–0.50	[14,16-17,19,23-24]
Burkholderia cepacia	89	0.016	0.12–0.50	[16]

[a]: total number of strains were obtained from cefiderocol surveillance project in corresponding references.

2.1.2 头孢地尔耐药性的产生

临床已有分离出头孢地尔耐药株的报道[9]。患者无头孢地尔暴露史，菌株产生的耐药机制可能由相关酶如 AmpC 酶编码基因氨基酸位点突变所致[25]。临床分离出的头孢地尔不敏感阴沟肠杆菌复合体可能与 AmpC 酶 R2 环氨基酸位点 A294_P295del 和 A292_L293del 突变有关。因头孢地尔与头孢他啶具有化学结构的相似性，AmpC 酶基因突变导致 R2 环 H-9 和 H-10 螺旋结构变化，从而增加了 AmpC 酶对头孢菌素类 (头孢吡肟、头孢他啶、头孢地尔) 的水解能力[25-26]。

临床挽救性治疗药物头孢他啶/阿维巴坦与头孢地尔可能存在一定的交叉耐药性[27]。通过对携带 bla_{KPC-3} 或 bla_{KPC-2} 基因的肺炎克雷伯菌进行体外诱导头孢他啶/阿维巴坦的耐药性发现，bla_{KPC} 基因发生氨基酸位点的点突变或框移突变。将含突变位点的酶基因克隆导入 pBR322 质粒中并在大肠埃希菌 TOP10 中克隆表达，75.6% (25/37) 克隆表达株头孢地尔的 MIC 值升高了 4–32 倍；而克隆转化 KPC-31 (D179Y-H274Y) 的菌株头孢地尔 MIC 值上升最高，达 4 μg/mL[27]。头孢地尔同时存在接种效应，即将接种菌量由 10^5 CFU/mL 升高 100 倍 (升至 10^7 CFU/mL)，头孢地尔的 MIC 值增加至>32 μg/mL[27]，检测菌株由敏感变为耐药。因此，应高度关注由高接种菌量 (10^7 CFU/mL) 引起的临床感染[27]，使用该药治疗时可能导致临床治疗的失败。

此外，铁转运蛋白的缺失对头孢地尔的体外抗菌活性影响也较大。当大肠埃希菌同时敲除铁转运蛋白 *cirA* 和 *fiu* 基因时，头孢地尔的 MIC 值较其亲体株升高了 16 倍 (由 0.06 μg/mL 上升至 1.00 μg/mL)[8]。当敲除铜绿假单胞菌 PAO1 的 *piuA* 基因时，头孢地尔的 MIC 值较其亲体株升高了 16 倍 (由 0.5 μg/mL 上升至 8.0 μg/mL)[28]。临床应用头孢地尔治疗由产 bla_{NDM-5} 和 bla_{OXA-48} 的阴沟肠杆菌 (头孢地尔 MIC 值为 2–4 μg/mL) 引起的腹腔感染和血流感染患者时，治疗 21 d 后分离出头孢地尔高水平耐药临床株 (≥256 μg/mL)，经全基因组测序分析发现铁载体受体蛋白 *cirA* 基因部分氨基酸位点的缺失或插入与头孢地尔耐药的快速进展密切相关[29]。

2.2 革兰阳性菌和厌氧菌

头孢地尔对革兰阳性菌和厌氧菌的体外抗菌活性较弱。粪肠球菌 ATCC29212、金黄色葡萄球菌 ATCC29213、干酪乳杆菌 ATCC393 和枯草芽孢杆菌 ATCC6633 头孢地尔的 MIC 均 ≥ 32 μg/mL[8]。头孢地尔对肺炎链球菌 ATCC49619 和化脓链球菌 ATCC10389 有体外抗菌活性，MIC 值分别为 2 μg/mL 和 1 μg/mL[8]。头孢地尔对于拟杆菌属、普雷沃菌属和艰难拟梭菌的 MIC_{90} 值均≥32 μg/mL[8]。细菌单层膜结构和铁载体运输系统的缺乏可能是革兰阳性菌和厌氧菌菌株高 MIC 值的原因。

2.3 头孢地尔对生物膜的影响

头孢地尔可通过影响铁载体受体蛋白摄取铁而有效地减少细菌生物膜的形成。无论在乏铁的阳离子调节肉汤还是阳离子调节肉汤均能抑制革兰阴性杆菌的浮游生长。随着头孢地尔用药浓度由 0 增长至 32 μg/mL，头孢地尔以剂量依赖方式抑制多重耐药革兰阴性杆菌，如铜绿假单胞菌、肺炎克雷伯菌、大肠埃希菌、鲍曼不动杆菌、洋葱伯克霍尔德菌复合体和嗜麦芽窄食单胞菌生物膜的形成[30]。相比于亚胺培南、头孢洛扎/他唑巴坦和妥布霉素，头孢地尔具有较好的降低铜绿假单胞菌生物膜形成的活性 (93% vs. 49%–82%)[30]。

2.4 头孢地尔联合其他抗菌药物的体外活性

通过时间杀菌曲线研究发现，头孢地尔联

合左氧氟沙星、米诺环素、多粘菌素 B 或复方新诺明分别对 4/9 (44.4%)、6/9 (66.7%)、5/9 (55.5%) 和 6/9 (66.7%) 左氧氟沙星和/或复方新诺明不敏感嗜麦芽窄食单胞菌具有协同作用[31]。头孢地尔联合 4 μg/mL 阿维巴坦 (丝氨酸酶抑制剂)和 100 μg/mL 吡啶二羧酸 (金属酶抑制剂)，可使携带 bla_{NDM} 的肺炎克雷伯菌头孢地尔 MIC 值从 4 μg/mL 降至 0.06–0.50 μg/mL[11]。对产 ESBLs 和/或 AmpC 酶的肠杆菌目细菌、携带 $bla_{OXA\text{-}50\text{-}like}$ 基因和产 AmpC 酶的铜绿假单胞菌和携带 $bla_{OXA\text{-}23}$ 和/或 $bla_{OXA\text{-}66}$ 基因的鲍曼不动杆菌，联用 4 μg/mL 阿维巴坦可使头孢地尔 MIC 值降低 8–128 倍[11]。

3 药代动力学及药效学

3.1 药代动力学

头孢地尔为时间依赖性药物，人和小鼠的血浆蛋白结合率分别为 58%[31] (40%–60%, https://www.drugs.com/ppa/cefiderocol.html) 和 47%[31]，该药主要与白蛋白结合。头孢地尔在健康人中平均血浆半衰期为 1.98–2.74 h，该药物主要在尿中以原型排泄[32]，约占给药剂量的 90.6%[33]。在健康受试者中，单剂量静脉注射 1 000 mg [^{14}C]标记的头孢地尔 (滴注时间为 1 h)，尿液和粪便中总放射性累计排泄率为 98.7%和 2.9%[33]。

健康成年男性单剂量 2 h 内静脉注射 2 000 mg 头孢地尔，1–6 h 内肺泡上皮内衬液头孢地尔的浓度与其血浆浓度平行变化，头孢地尔可以从血浆迅速分布到肺泡上皮内衬液[34]，表明头孢地尔可用于治疗医院获得性肺炎。

统计显示，头孢地尔血浆半衰期 (terminal elimination half-life, $t_{1/2}$)、总清除率 (total clearance, CL)、平均滞留时间 (mean residence time, MRT)、用药 48 h 尿排泄率 ($Feu_{0–48}$) 和肾清除率 (renal clearance, CL_R) 与用药剂量 (100 mg、250 mg、500 mg、1 000 mg 和 2 000 mg 单剂量注射组) 无关[32]。头孢地尔的 CL 和 $t_{1/2}$ 与肾脏功能相关。随着肾损害程度的增加，头孢地尔血浆浓度峰值不发生显著改变，但其半衰期 $t_{1/2}$ 不断延长，药时曲线下面积 (area under the concentration-time curve, AUC) 增加，CL 依次下降[35]。因此，肾功能正常的危重症患者，使用头孢地尔标准剂量 2 g、1 次/8 h (以 q8h 表示)，3 h 内输注[36]治疗头孢地尔 MIC 值≤4 μg/mL 的菌株感染时，>90%可达到达标概率 (target attainment, PTA, 75% $T_{f>MIC}$)。对于肾功能受损的患者，需要根据肾功能调整剂量。间歇性血液透析的患者在间歇性血液透析后需立即给予补充剂量。对肾功能增强 (Cockcroft- Gault-$CL_{creatinine}$, CG-CL_{CR}>120 mL/min) 的患者可增加给药频次，如 1 次/6h (q6h)[36]。构建铁缺乏的动物模型显示，乏铁条件下头孢地尔药代动力学发生变化，血药浓度小幅度下降，应适当增加用量[37]。

3.2 药效学

抗菌药物药效学存在 3 种与临床疗效相关的参数，游离血药峰浓度与 MIC 的比值 (free peak level divided by the MIC, fC_{max}/MIC)、24 h 内游离血药浓度-时间曲线下面积与 MIC 的比值 (area under the free concentration-time curve over 24 h divided by the MIC, fAUC/MIC) 和 24 h 内游离血药浓度超过 MIC 的累积时间百分比 (cumulative percentage of a 24 h period that the free drug concentration in plasma exceeds the MIC, %fT>MIC)，其中%fT>MIC 是评价头孢地尔体内抗菌效果最相关的参数[38]。头孢地尔对不同 MIC 值的菌株发挥的抗菌能力不同。在小鼠大腿感染模型中，对于头孢地尔 MIC

值≤4 μg/mL 的菌株，77%的肠杆菌目细菌、88%的鲍曼不动杆菌和 85%的铜绿假单胞菌被抑制生长或细菌菌落计数下降≥10 倍[39]。而对于头孢地尔 MIC 值≥8 μg/mL 的菌株，只有 2 株出现细菌生长停滞或细菌菌落计数下降≥10 倍[39]。

输注 β-内酰胺类药物的持续时间会影响%*f*T>MIC[40]，通过延长药物滴注时间或增加给药频次可以改善 β-内酰胺类抗菌药物的药效学特征[40]。在中性粒细胞减少的小鼠大腿感染模型中，头孢地尔延长暴露 72 h 内可表现出持续的抗菌活性[41]。根据小鼠模型推测，当给药剂量为 2 g q8h 时，头孢地尔的 MIC 值为≤2 μg/mL 时，静脉输注 1 h，人体%*f*T>MIC 可达 100%；当头孢地尔的 MIC 值为 4 μg/mL 时，给药时间 1 h 和 3 h，人体%*f*T>MIC 分别为 75%和 100%；当头孢地尔的 MIC 值为 8 μg/mL 时，持续 3 h 输注可保持%*f*T>MIC 为 100%[31]。

4 头孢地尔临床治疗有效性和安全性

表 2 列出了头孢地尔用于临床治疗的案例报道。应用头孢地尔治疗泛耐药鲍曼不动杆菌和产 KPC 酶肺炎克雷伯菌的血流感染具有良好疗效，经过 14 d 头孢地尔治疗，患者获得了临床治愈并实现微生物学清除[42]。使用 750 mg、1 次/12 h (q12h) 头孢地尔加 500 mg q8h 甲硝唑的联合治疗方案，成功地治愈了多重耐药性铜绿假单胞菌引起的腹腔内感染[43]。此外，头孢地尔也对泛耐药无色杆菌导致的肺部感染[44]、多重耐药木糖氧化无色杆菌导致的化脓性气管支气管炎合并持续菌血症[45]、多重耐药铜绿假单胞菌导致主动脉瓣心内膜炎合并持续性菌血症[46]、肺炎克雷伯菌导致的腹腔感染合并血流感染[47]、胸瘘伴多重耐药铜绿假单胞菌引起的积脓[48]、CRE 与多重耐药鲍曼不动杆菌或多重耐药铜绿假单胞菌引起的骨髓炎及骨关节感染[37,49-50]以及外科手术或假体相关感染[45,49,51-52]具有较好的临床疗效，患者症状好转。为防止抗菌药物滥用产生耐药性，使用头孢地尔治疗前，应对头孢地尔进行体外敏感性检测[53]。头孢地尔用于临床治疗仍需更多的临床研究。

表 3 展示了有关头孢地尔的Ⅱ期、Ⅲ期临床试验研究结果。2016–2019 年在南美洲、北美洲、亚洲和欧洲 16 个国家 95 家医院开展了头孢地尔治疗碳青霉烯耐药革兰阴性杆菌引起的院内获得性肺炎、血流感染/脓毒症或复杂性尿路感染的安全性和有效性研究的Ⅲ期临床试验 (CREDIBLE-CR)[54]。头孢地尔治疗组和最佳治疗组分别为 101 例和 51 例。最佳治疗组包括以粘菌素为基础的抗菌药物组合或非粘菌素组合。在 118 例靶向治疗患者中，由鲍曼不动杆菌引起的感染占 46% (54/118)，肺炎克雷伯菌占 33% (39/118)，铜绿假单胞菌占 19% (22/118)。院内获得性肺炎和血流感染/脓毒症患者中，头孢地尔治疗组与最佳治疗组达到的临床治愈率相当；而在复杂性尿路感染患者中头孢地尔相比于最佳方案治疗组表现出较高的微生物学清除率，分别为 53% (9/17) 和 20% (1/5)[54]。

2015–2016 年，15 个国家 65 个中心进行了头孢地尔 (2 g q8h, 7–14 d) 与亚胺培南/西司他丁 (1 g q8h, 7–14 d) 治疗革兰阴性杆菌导致的复杂性尿路感染的非劣效Ⅱ期临床试验 (APEKS-cUTI)。研究发现，头孢地尔治疗组和对照组的临床治愈率分别为 73% (183/252) 和 55% (65/119)，微生物学清除率分别为 73% (184/252) 和 56% (67/119)[55]。2017–2019 年在亚洲、欧洲

表 2　头孢地尔治疗多重耐药革兰阴性杆菌感染的临床研究

Table 2　Clinical trials study on cefiderocol treatment against multi-drug resistant Gram-negative bacilli infections

Country	Infections	Patients	Underlying disease	Resistant pathogens	Other susceptible drugs	Cefiderocol MIC (mg/L) or KB (mm)	Resistant genes	Drug regimen	Outcome	Adverse reactions	References
Italy	Bacteremia secondary to ventilator associated pneumonia	Adult/M	Severe H1N1 influenza, Favism and Aarskog-Scott syndrome	XDR-*A. baumannii* and *K. pneumoniae*	Colistin	23 mm (S, blood), 22 mm (S, surveillance swab)	bla_{KPC} (*K. penumoniae*)	Cefiderocol+linezolid, 14 d	Clinical cure and bacterial clearance	None	[42]
USA	Pulmonary infection	10y/F	Cystic fibrosis	PDR-*Achromobacter* spp.	None[a]	32 mg/L (R)	-	Course 1: cefiderocol (3 h, 60 mg/kg, q8h, iv. over 3 h, 21 d)+ meropenem/vaborbactam (2 g q8h, over 3 h, 14 d), and then bacteriophage (qd, iv. over 1 h) for 14 d; Course 2: cefiderocol (3 h, 60 mg/kg, q8h, iv. over 3 h, 12 d)+ meropenem/vaborbactam (2 g q8h, over 3 h, 12 d)+ bacteriophage (qd, iv. over 1 h, 12 d)	Clinical cure and bacterial clearance	None	[44]
Spain	Purulent tracheobronchitis, persisting bacteremia	66y/M	Refractory chronic heart failure received a left ventricular assist device, lung adenocarcinoma	MDR-*Achromobacter xylosoxidans*	–	21 mm (S)	–	Cefiderocol (2g q8h, iv. over 3 h, 14 d)+ piperacillin/tazobactam (4.5 g q6h, 42 d)+ tigecycline (100 mg q12h, 42 d)	Clinical improved[c]	Thrombocytopenia	[48]
UK	Persistent bacteremia, aortic valve endocarditis	78y/F	Thickened aortic valve, cerebral infarction, breast cancer remission	*P. aeruginosa*	Colistin, amikacin, gentamicin	21.3 mm (S)	bla_{VEB}	Cefiderocol (2 g q8h, iv. Over 3 h, 2 d; then 2 g q12h, 30 d)+meropenem (2 g, q12h, 9 d)+colistin (9MU loading dose, 3 MU q8h, subsequently 4.5 MU, q12h, 30 d) + aortic valve replacement	Clinical cure and bacterial clearance	Neutropenia	[46]
USA	Abdominal infection, bacteremia	68y/F	Kidney post-transplant, end-stage renal disease secondary to diabetes mellitus	*K. pneumoniae*	Colistin, tigecycline, eravacycline	22 mm (S, blood), 21 or 22 mm (S, abdominal drainage, kidney allograft and hematoma)	bla_{NDM-1} and $bla_{OXA-232}$	Cefiderocol (1.5 g q12h, 12 d)+polymyxin B (19 d)+ceftazidime/ avibactam (18 d)+ aztreonam (10 d)+ tigecycline (3 d)	Death and bacterial clearance	–	[47]
USA	Intraabdominal abscess	46y/M	Hemodialysis for end-stage renal disease secondary to diabetes mellitus	MDR-*P. aeruginosa*	Amikacin, colistin	0.12 mg/L (S)	None[b]	Cefiderocol 0.75 g q12h, 28 d+surgical management	Clinical cure	None	[43]

(待续)

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(续表 2)

Country	Infections	Patients	Underlying disease	Resistant pathogens	Other susceptible drugs	Cefiderocol MIC (mg/L) or KB (mm)	Resistant genes	Drug regimen	Outcome	Adverse reactions	References
USA	Empyema	45y/F	Hemangioblastoma, esophageal-pleural fistula	XDR-*P. aeruginosa*	Amikacin, colistin	0.25 mg/L (S)	–	Cefiderocol (2 g q8h, iv. over 3 h, 3 w)	Clinical cure but microbiological failure	None	[48]
Thailand	Pleural empyema, acute osteomyelitis	62y/M	None	XDR-*A. baumannii*	Colistin	20 mm (S)	bla_{OXA-23}; bla_{OXA-58}	Course 1: cefiderocol (2 g q8h, iv. over 3 h, 14 d; 1.5 g q8h, 18 d)+colistin (14 d); Course 2: cefiderocol (2 g q8h, iv. over 3 h, 6 w)	Clinical cure and bacterial clearance	None	[49]
USA	Chronic osteomyelitis	15y/M	None	XDR-*P. aeruginosa* and *K. pneumoniae*	Colistin	4 mg/L (S); 0.5 mg/L (S)	bla_{NDM-1}; ESBL	Cefiderocol (2 g q8h, iv. over 3 h, 14 w, prolonged course)+a bone graft and antibiotic nail exchange	Clinical cure and bacterial clearance	Intermittent episodes of decreased white cell counts	[37]
USA	Osteomyelitis	57y/M	Type 2 diabetes mellitus and hypertension	XDR-*A. baumannii*	Colistin, fosfomycin	23 mm (S)	bla_{OXA-23} and bla_{OXA-66}	Cefiderocol (1 g q8h, 5 d; 2 g q8h, iv. over 3 h, 104 d)	Clinical cure and bacterial clearance	None	[50]
Columbia	Acute vertebral osteomyelitis	29y/M	None	*P. aeruginosa*, *A. baumannii*, *E. cloacae*	Colistin	24 mm (S); 23 mm (S); 14 mm (S)	bla_{VIM}; bla_{OXA-23}; bla_{KPC}	Cefiderocol (2 g q8h, iv. over 3 h, 14 d)+ cetazidime/avibactam (4 w)+colistin (4 w)	Clinical cure and bacterial clearance	None	[49]
Serbia	Postoperative implant-associated surgical site infection	64y/M	None	*A. baumannii*	Colistin	18 mm (S)	bla_{NDM} and bla_{OXA-40}	Cefiderocol (2 g q8h, iv. over 3 h, 11 d)+colistin (11 d) after surgical revision, then cefiderocol (1.5 g q8h 1 w), cefiderocol (2 g q8h, iv. over 3 h, 6 w)	Clinical cure and bacterial clearance	None	[49]
France	Knee prosthetic joint infection	67y/M	Atrial fibrillation on anticoagulant	XDR-*Enterobacter hormaechei* subsp. *hoffmaniis*	Tigecycline, colistin ceftazidime/ avibactam, imipenem/ relebactam, meropenem/ vaborbactam, evaracycline	1 mg/L (S)	$bla_{CTX-M-15}$ bla_{TEM-1B}, bla_{OXA-1} and bla_{ACT-5}	Cefiderocol (2 g q8h, iv. over 3 h, 10 w)	Clinical cure	None	[51]
Spain	Portal prosthesis infection, bacteremia	55y/M	Portal revascularization, renal transplant history	XDR-*P. aeruginosa*	–	23 mm (S)	–	Cefiderocol (2 g q8h, iv. over 3 h, 6 w)+colistin (3 MU q8h, 2 w)	Clinical cure and microbiological clearance	None	[45]
Italy	Neurosurgical site infection with s subcutaneous abscess, parietal bone osteomyelitis	64y/M	Arterial hypertension, post-surgical hypothyroidism	XDR-*P. aeruginosa*	Colistin, fosfomycin	0.5 mg/L (S)	–	Cefiderocol (2 g q8h, iv. over 3 h, 14 d)+ Fosfomycin (6 g, q8h, 14 d)	Clinical cure	none	[54]

S: susceptible; R: resistant.

表 3 头孢地尔 vs 其他抗菌药物治疗的临床试验 (年龄≥18 岁)

Table 3 Clinical trials on cefiderocol vs other antimicrobial therapy regimens (Age≥18 years)

Project	CREDIBLE-CR	APEKS-NP	APEKS-cUTI
Year	2016.9.7–2019.4.22	2017.10.23–2019.4.14	2015.2.5–2016.8.16
Study type	Phase III, randomized, open-label trail	Phase III, randomized, double-blind, non-inferiority trial	Phase II, randomized, double-blind, non-inferiority trial
Study centers	95 hospitals in 16 countries in South America, North America, Europe and Asia	76 centers in 17 countries in Asia, Europe and the United States	67 hospitals in 15 countries
Infections	Nosocomial pneumonia, bloodstream infection (BSI) or sepsis, complicated urinary tract infection (cUTI)	Hospital-acquired, ventilator-associated or health-care-associated pneumonia	cUTI with or without pyelonephritis or those with acute uncomplicated pyelonephritis
Pathogens	Carbapenem-resistant Gram-negative bacilli, including *A. baumannii*, *K. Pneumoniae*, *P. aeruginosa*, *S. maltophilia*, *A. nosocomialis*, *E. cloacae*, *E. coli*	*K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, *E. coli*, *E. cloacae*, *S. maltophilia*	*E. coli*, *K pneumoniae*, *P. aeruginosa*, *Proteus mirabilis*, *E. cloacae* complex, etc.
Treatment regime	Cefiderocol vs. best-available treatment (2:1)	Cefiderocol vs. high dose, extended-infusion meropenem (1:1)	Cefiderocol vs. imipenem/cilastatin (2:1)
Dose and course	Cefiderocol (2 g q8h, 7–14 d)	Cefiderocol (2 g q8h, over 1 h, 7–14 d vs. meropenem (2 g q8h, 7–14 d)	Cefiderocol (2 g q8h, over 1 h, 7–14 d vs. imipenem/cilastatin (1 g q8h, 7–14 d)
Case load	Nosocomial pneumonia: 45 vs. 22 BSI or sepsis: 30 vs. 17 cUTI: 26 vs. 10	148 vs. 150	300 vs. 148
Clinical cure rate (%)	Nosocomial pneumonia: 50% (20/40) vs. 53% (10/19) BSI or sepsis: 43% (10/23) vs. 43% (6/14) cUTI: 71% (12/17) vs. 60% (3/5)	65% (94/145) vs. 67% (98/147)	73% (183/252) vs. 55% (65/119)
Microbial eradication rate (%)	Nosocomial pneumonia: 23% (9/40) vs. 21% (4/19) BSI or sepsis: 30% (7/23) vs. 29% (4/14) cUTI: 53% (9/17) vs. 20% (1/5)	41% (59/145) vs. 42% (61/147)	73% (184/252) vs. 56% (67/119)
Adverse event rate (%)	91% (92/101) vs. 96% (47/49)	88% (130/148) vs. 86% (129/150)	41% (122/300) vs. 51% (76/148)
Treatment-emergent adverse events	Diarrhoea, pyrexia, septic shock, vomiting, decubitus ulcer, hypokalaemia, liver function test abnormal, constipation, hypotension, anaemia, aspartate aminotransferase increase, pleural effusion, acute kidney injury, dyspnoea, nausea, pneumonia, alanine aminotransferase increased, abdominal pain, hypomagnesaemia, thrombocytopenia, chest pain, hyperkalaemia, agitation, oedema peripheral, sepsis, rash, bradycardia, metabolic acidosis, insomnia	Urinary tract infection, hypokalaemia, diarrhoea, anaemia, pneumonia, aspartate aminotransferase increased, pleural effusion, alanine aminotransferase increased, hypomagnesaemia, hypoalbuminaemia, hepatic enzyme increased, hyponatraemia, decubitus ulcer, hypotension, thrombocytopenia	Diarrhoea, hypertension, constipation, infusion site pain, headache, nausea, cough, vomiting, hypokalemia, insomnia, renal cyst, infusion site erythema, abdominal pain upper, cardiac failure, clostridium difficile colitis or vaginal infection
All-cause mortality	19% (19/101) vs. 12% (6/49) at Day 14 25% (25/101) vs. 18% (9/49) at Day 28	12.4% (18/145) vs. 11.6% (17/146) at Day 14 21.0% (30/143) vs. 20.5% (30/146) at Day 28	–
References	[54]	[56]	[55]

和美国进行了 17 个国家 76 个中心的随机、双盲头孢地尔Ⅲ期临床研究 (APEKS-NP), 比较了头孢地尔 (2 g q8h, 7–14 d) 和高剂量美罗培南延长滴注时间 (2 g q8h, 7–14 d) 在治疗革兰阴性杆菌导致的医院获得性肺炎患者中的临床疗效。两种方案具有相当的微生物学清除率和临床治愈率[56]。

头孢地尔治疗组与最佳治疗组、高剂量美罗培南长时间滴注组和亚胺培南/西司他丁治疗组相比，不良事件的发生率相近[54-56]。Ⅲ期临床试验中，CREDIBLE-CR 与 APEKS-NP 在治疗诱发的紧急不良事件均表现出腹泻 (19% vs. 8.8%)、丙氨酸转氨酶升高 (7% vs. 6.1%)、天冬氨酸转氨酶升高 (8% vs. 6.8%)、肺炎 (7% vs. 7.4%)、贫血 (8% vs. 8.1%) 和胸腔积液 (8% vs. 6.8%)[54,56]。此外，CREDIBLE-CR 治疗诱发的紧急不良事件 (≥8%) 还表现为发热 (14%)、感染性休克 (13%)、呕吐 (13%)、褥疮 (10%)、便秘 (9%)、低血压 (8%)[54]；APEKS-NP 的Ⅲ期临床试验中，治疗诱发的紧急不良事件 (发生概率≥6%) 还表现为尿路感染 (15.5%)、低钾血症 (10.8%)。无论是Ⅱ期还是Ⅲ期临床试验，头孢地尔都表现出较好的耐受性。

5 总结与展望

研发新药是对抗多重耐药革兰阴性杆菌的重要手段之一。2019 年美国新上市的新型铁载体头孢菌素头孢地尔，对包括金属酶在内的几乎所有 β 内酰胺酶具有较好的稳定性，对碳青霉烯耐药的革兰阴性杆菌引起的严重感染具有较好的临床疗效。此外，头孢地尔具有较好的安全性和耐受性。在治疗腹腔感染、骨关节感染、血流感染、复杂性尿路感染和肺部感染中，头孢地尔具有较好的临床治疗成功率和微生物学清除率。头孢地尔有望成为治疗由多重耐药革兰阴性杆菌引起感染的强有力的选择。此外，头孢地尔通过铁载体转运蛋白在细菌周浆间隙富集的转运方式为新药的开发提供了新思路。

头孢地尔发挥对抗革兰阴性杆菌生物膜活性的机制尚不清楚，其是否在生物膜环境中通过铁载体转运途径增加头孢地尔的渗透，仍需要进一步转录组学和共定位的研究[30]。目前关于头孢地尔体外联合用药的研究较少，仍需对头孢地尔联合其他抗菌药物的协同抗菌作用进行大批量体内外试验验证。

头孢地尔临床菌株耐药率较低，但不容忽视。铁载体转运系统突变、与头孢他啶/阿维巴坦的交叉耐药性和接种效应均提示临床治疗时，应密切关注头孢地尔的体外药敏结果。头孢地尔应作为挽救性治疗措施，谨防抗菌药物滥用产生耐药性。总之，头孢地尔作为新型铁载体头孢菌素在治疗多重耐药革兰阴性杆菌感染中具有较好的应用前景。

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