Vol. 41 No. 24 December 2025(Serial No. 446)

临床与基础
桥接研究
Clinical and Basic
Bridging Research

头孢比罗体外抗菌作用研究

Study on *in vitro* activity of ceftobiprole

薛 峰, 张 佳, 李 耘

(北京大学 第一医院 临床药理研究所, 北京 100034)

XUE Feng, ZHANG Jia,
LI Yun

(*Institute of Clinical Pharmacology, Peking University First Hospital, Beijing 100034, China*)

摘要:目的 评价头孢比罗对近年临床常见分离菌的体外抗菌活性。**方法** 最低抑菌浓度(MIC)测定采用标准微量肉汤二倍稀释法。**结果** 对2019~2020年间全国范围内临床分离948株细菌进行了MIC测定。结果显示:头孢比罗对革兰阳性菌具有很好抗菌作用,对甲氧西林敏感葡萄球菌 MIC_{90} 值为0.5 mg·L^{-1}。甲氧西林耐药金黄色葡萄球菌(MRSA)对其敏感率为93.1%,优于头孢洛林(72.3%)。头孢比罗对青霉素不敏感肺炎链球菌(PNSSP)MIC值在0.06~1 mg·L^{-1},细菌敏感率为80.0%;对其他链球菌及粪肠球菌 MIC_{90} 值≤2 mg·L^{-1}。革兰阴性菌中,头孢比罗对超广谱β-内酰胺酶(ESBLs)阴性大肠埃希菌、肺炎克雷伯菌以及氨苄西林敏感流感嗜血杆菌、卡他莫拉菌同样具有很好抗菌作用,MIC_{90} 值≤0.5 mg·L^{-1},菌株敏感率≥98.1%。头孢比罗对铜绿假单胞菌抗菌作用与头孢他啶、头孢吡肟相似。**结论** 头孢比罗对国内近年临床分离常见革兰阳性、阴性致病菌,包括MRSA、PNSSP等均有很好抗菌作用,与欧美监测结果相似。临床前景值得期待。

关键词:头孢比罗;体外;最低抑菌浓度
DOI:10.13699/j.cnki.1001-6821.2025.24.007
中图分类号:R978 **文献标志码:**A
文章编号:1001-6821(2025)24-3491-08

Abstract: Objective To evaluate *in vitro* activity of ceftobiprole against clinical isolated bacteria in recent years in China. **Methods** The minimal inhibitory concentrations (MICs) were determined by the microbroth dilution method. **Results** A total of 948 clinical isolates collected from nationwide between 2019 to 2020 were studied. Ceftobiprole exhibited excellent antibacterial activity against gram-positive cocci, the value of MIC_{90} was 0.5 mg·L^{-1} for methicillin susceptible *Staphylococcus* spp and susceptibility rates of methicillin resistant *Staphylococcus aureus* (MRSA) were 93.1%, which was better than that of ceftaroline (72.3%). The MIC values of ceftobiprole against penicillin nonsusceptible *Streptococcus pneumoniae* (PNSSP) ranged from 0.06 to 1 mg·L^{-1}, with 80.0% susceptibility rate. The values of MIC_{90} of ceftobiprole were ≤2 mg·L^{-1} for other streptococci and *Enterococcus faecalis*. Against Gram-negative bacteria, ceftobiprole also showed better antibacterial activity against non-extended spectrum β-lactamases (ESBLs) *Escherichia coli*, non-ESBLs *Klebsiella pneumoniae*, ampicillin-susceptible *Haemophilus influenzae* and *Moraxella catarrhalis*, the values of MIC_{90} ≤0.5 mg·L^{-1} and susceptible strains more than 98.1%. The activity of ceftobiprole against *Pseudomonas aeruginosa* was similar to that of ceftazidime and cefepime.

作者简介:薛峰(1971-),男,主管技师,主要从事抗菌药物临床前药效研究
通信作者:李耘,副研究员
Tel:(010)82802440
E-mail:liyun19702@sina.com

Conclusion Ceftobiprole showed excellent antibacterial activity against clinical isolates, include MRSA, PNSSP, and *Haemophilus influenzae* in recent years in China, which similar to the surveillance results in Europe and America. The clinical prospect is worthy of expectation.

Key words: ceftobiprole; *in vitro*; minimal inhibitory concentration

头孢比罗(ceftobiprole,曾译名:头孢吡普)为体外对甲氧西林耐药金黄色葡萄球菌(methicillin resistant *Staphylococcus aureus*, MRSA)和万古霉素耐药金黄色葡萄球菌(vancomycin resistant *Staphylococcus aureus*, VRSA)有效的头孢菌素类抗生素中第一个完成Ⅲ期临床试验的药物[1],2008年先后在加拿大、瑞士上市用于治疗包括糖尿病足感染在内的复杂性皮肤及皮肤软组织感染[2]。此外,在欧洲多个国家被批准用于治疗成人社区和医院获得性肺炎(除外机械通气相关肺炎)[3]。其作用机制同其他β-内酰胺类抗生素,通过作用于青霉素结合蛋白(penicillin binding proteins, PBP),干扰细胞壁合成而发挥抗菌作用。头孢比罗与多种PBP均能结合,与MRSA耐药相关的PBP2a具有高度亲和力是其对耐药革兰阳性菌具有强效抗菌活性的原因[4-5],而与大肠埃希菌、铜绿假单胞菌PBPs的高亲和力使其对革兰阴性菌也有很好抗菌活性[6]。因此,头孢比罗在临床抗感染治疗中将会成为重要选择,但其对国内临床分离致病菌体外抗菌活性研究较少,本研究旨在评价头孢比罗对近年国内临床常见分离菌的体外抗菌作用。

材料与方法

1 材料

药品 头孢比罗,规格:每支250 mg,批号:08004R25F,效价:90.8%,深圳华润九新药业有限公司生产;头孢洛林,规格:每支100 mg,批号:118543,效价:96.51%,美国MCE公司生产;头孢曲松,规格:每支200 mg,批号:130480-201504,效价:83.9%;头孢他啶,规格:每支100 mg,批号:130484-201806,效价:85.8%;头孢吡肟,规格:每支100 mg,批号:130524-200502,效价:83.0%;青霉素,规格:每支100 mg,批号:130437-200904,效价:88.8%;苯唑西林,规格:每支500 mg,批号:0482-9901,效价:90.4%;万古霉素,规格:每支150 mg,批号:130360-201302,效价:1066 μ·mg^{-1};均由中国食品药品检定研究院或中国药品生物制品检定所生产;氨苄西林,规格:每支5 g,批号:R1/69/339,效价:87.5%,意大利INALCO公司生产;利奈唑胺,规格:每支1 g,批号:20160408,效价:89.7%,德国拜耳公司生产;达托霉素药敏板,批号:VD12148,温州市康泰生物科技有限公司生产。

标准质控菌株 金黄色葡萄球菌ATCC 29213,粪肠球菌ATCC 29212,肺炎链球菌ATCC 49619,大肠埃希菌ATCC 25922,铜绿假单胞菌ATCC 27853,流感嗜血杆菌ATCC 49247。

临床分离菌株 共948株,收集时间为2019年7月1日至2020年6月30日,同一患者分离的相同菌株取第1株。

2 培养基与孵育条件

链球菌为含5%裂解马血阳离子调节MH肉汤(cation-adjusted Mueller-Hinton broth, CAMHB)培养基,(35±2)℃孵育20~24 h;嗜血杆菌为嗜血杆菌试验培养基(Haemophilus test medium, HTM),(35±2)℃孵育20~24 h;其他菌种为CAMHB培养基,(35±2)℃孵育16~20 h(含苯唑西林培养基中加入2% NaCl,孵育24 h)。

3 最低抑菌浓度(minimum inhibitory concentration,MIC)测定

用标准微量肉汤二倍稀释法。抗菌药物测定浓度范围256~0.002 mg·L^{-1}(头孢洛林浓度范围:32~0.002 mg·L^{-1})。菌液终浓度为5×10^5 CFU·mL^{-1}。每株细菌在试验前经过平板转活分纯,以新鲜菌体用于试验。每次试验用标准菌株作为敏感试验质控菌;不含抗菌药物的菌液孔做为试验菌株生长对照。头孢比罗按照美国食品药品监督管理局(US Food and Drug Administration, FDA)2024年颁布折点[7](包括金黄色葡萄球菌、肺炎链球菌、化脓链球菌、大肠埃希菌、肺炎克雷伯菌和流感嗜血杆菌)计算细菌敏感、耐药率;其他药物按照美国临床和实验室标准化协会(Clinical and Laboratory Standards Institute, CLSI)2024折点[8]计算。对于卡他莫拉菌,测定药物均以欧洲抗微生物药物敏感性试验委员会(European Committee on Antimicrobial Susceptibility Testing, EUCAST)2024标准[9]计算。每一MIC值对应的累积抑菌百分比以小于等于此MIC值菌株数除以总测试菌株数×100%计算获得。

结　果

1　头孢比罗及对照药物对革兰阳性菌 MIC 结果

头孢比罗对革兰阳性菌具有很好抗菌作用,对甲氧西林敏感葡萄球菌(methicillin susceptible *Staphylococcus aureus*, MSSA)90% 最低抑菌浓度(90% minimum inhibitory concentration, MIC_{90})值为 0.5 mg·L^{-1},甲氧西林敏感金黄色葡萄球菌对其敏感率为 100%。对 MRSA 和甲氧西林耐药表皮葡萄球菌(methicillin resistant *Staphylococcus epidermidis*, MRSE)的 MIC_{90}值≤2 mg·L^{-1},MRSA 对其敏感率为 93.1%。对甲氧西林耐药的其他凝固酶阴性葡萄球菌 MIC_{90}值为 8 mg·L^{-1},5 株耐药菌 MIC 值在8~16 mg·L^{-1},均为溶血葡萄球菌。头孢洛林对葡萄球菌 MIC 值与头孢比罗相似,对 MSSA 的累积抑菌百分比在 MIC 值为 0.25 mg·L^{-1}时略高于头孢比罗,对 MRSA 的累积抑菌百分比基本一致,见图 1 和图 2。MSSA 对头孢洛林 100% 敏感,MRSA 敏感率为 72.3%,略低于头孢比罗。万古霉素、利奈唑胺和达托霉素对葡萄球菌也具有很好抗菌作用,细菌敏感率≥89.8%,见表 1。

头孢比罗对青霉素敏感肺炎链球菌(青霉素 MIC ≤0.06 mg·L^{-1})具有很好抗菌作用,MIC 值≤0.06 mg·L^{-1},菌株 100% 敏感。累积抑菌百分比与头孢洛林基本一致,优于头孢曲松和利奈唑胺,见图 3。对青霉素不敏感肺炎链球菌,头孢比罗 MIC 值随之升高,在 0.06~1 mg·L^{-1},细菌敏感率为 80.0%,中介率 20%,无耐药。所测头孢菌素类药物均呈现此特征,对青霉素不敏感菌 MIC 众数较敏感菌升高32 倍,菌株对头孢洛林、头孢曲松、头孢吡肟敏感率分别为 100%、84.3% 和 61.4%。累积抑菌百分比图显示头孢比罗与头孢曲松相似,见图 4。万古霉素、利奈唑胺和达托霉素抗菌作用不受青霉素敏感与否影响,见表 1。

头孢比罗及对照药对化脓链球菌和无乳链球菌均具有很好抗菌活性,MIC 值≤0.03 mg·L^{-1}。草绿组链球菌对青霉素敏感率为 64.0%,青霉素、头孢曲松、头孢吡肟 MIC_{90}值≥16 mg·L^{-1}。头孢比罗、头孢洛林相对具有更好抗菌作用,MIC_{90} 值分别为 2 mg·L^{-1}和 1 mg·L^{-1}。

头孢比罗对粪肠球菌具有一定抗菌作用,MIC_{90} 值为 1 mg·L^{-1},较氨苄西林低 1 个稀释度。头孢洛林对粪肠球菌抗菌作用弱,利奈唑胺敏感率为 86.3%,万古霉素、达托霉素 100% 敏感。

2　头孢比罗及对照药物对革兰阴性菌 MIC 结果

头孢比罗对超广谱 β-内酰胺酶(extended spectrum β-lactamases, ESBLs)阴性大肠埃希菌、肺炎克雷伯菌同样具有很好抗菌作用,MIC_{90} 值为 0.06 mg·L^{-1},菌株敏感率分别为 100% 和 98.1%。头孢洛林 MIC 值普遍较头孢比罗高 1~2 个稀释度。其他所测第三、四代头孢菌素也对 ESBLs 阴性大肠埃希菌和肺炎克雷伯菌具有较好抗菌活性,累积抑菌百分比图显示头孢比罗与头孢吡肟相似,优于头孢洛林和头孢他啶,见表 2、图 5 和图 6。对氨苄西林敏感的流感嗜血杆菌,头孢比罗 MIC 值≤0.06 mg·L^{-1},菌株 100% 敏感,累积抑菌百分比略优于头孢吡肟,逊于头孢曲松和头孢洛林,见图 7;对氨苄西林耐药流感嗜血杆菌,头孢比罗 MIC 值有所上升,在 0.016~1 mg·L^{-1},耐药率 10.8%。头孢洛林对氨苄西林耐药流感嗜血杆菌 MIC_{90}值与头孢比罗相同,细菌不敏感率为 16.2%。头孢曲松、头孢他啶、头孢吡肟对流感嗜血杆菌抗菌活性同样受氨苄西林耐药与否影响,对耐药菌 MIC 值较敏感菌高 2 个稀释度以上,见表 2 和图 8。头孢比罗对卡他莫拉菌 MIC 值在 0.03~0.5 mg·L^{-1},其他对照药也具有很好抗菌作用。

头孢比罗对头孢他啶敏感铜绿假单胞菌 MIC_{50}、MIC_{90}值分别为 4 mg·L^{-1}和 8 mg·L^{-1},与头孢他啶、头孢吡肟相似。对头孢他啶不敏感铜绿假单胞菌,头孢比罗和头孢吡肟同样无抗菌作用。头孢洛林对铜绿假单胞菌无抗菌作用。

表 1　抗菌药物对革兰阳性菌 MIC 结果及细菌敏感、耐药率(%)

Table 1　Antibacterial activity and susceptibility (S) and resistance (R) rates (%) of antimicrobial agents against gram-positive cocci

Strains(Number)	Antibiotic	MIC_{50} (mg·L^{-1})	MIC_{90} (mg·L^{-1})	MIC_{mode} (mg·L^{-1})	MIC_{range} (mg·L^{-1})	S	R
MSSA(52)	Ceftobiprole	0.5	0.5	0.5	0.25-1	100	0
	Ceftaroline	0.25	0.5	0.25	0.25-0.5	100	0
	Oxacillin	0.5	1	0.5	0.25-1	100	0
	Vancomycin	1	1	1	0.5-1	100	0
	Linezolid	2	2	2	1-2	100	0
	Daptomycin	0.5	0.5	0.5	0.25-1	100	-

续表1(Continued tablet 1)

Strains(Number)	Antibiotic	MIC_{50} ($mg \cdot L^{-1}$)	MIC_{90} ($mg \cdot L^{-1}$)	MIC_{mode} ($mg \cdot L^{-1}$)	MIC_{range} ($mg \cdot L^{-1}$)	S	R
MRSA(101)	Ceftobiprole	1	2	1	0.5 – 4	93.1	0
	Ceftaroline	1	2	1	0.5 – 4	72.3	0
	Oxacillin	64	>256	>256	4 – >256	0	100
	Vancomycin	1	1	1	0.5 – 1	100	0
	Linezolid	2	2	2	1 – 2	100	0
	Daptomycin	0.5	0.5	0.5	0.25 – 1	100	–
MSSE(47)	Ceftobiprole	0.12	0.25	0.12	0.008 – 0.25	–	–
	Ceftaroline	0.06	0.12	0.06	0.008 – 0.12	–	–
	Oxacillin	0.12	0.5	0.06, 0.12	0.03 – 0.5	100	0
	Vancomycin	1	2	1	0.25 – 2	100	0
	Linezolid	1	1	1	0.25 – 2	100	0
	Daptomycin	0.25	0.25	0.25	0.06 – 1	100	–
MRSE(53)	Ceftobiprole	0.5	1	0.5	0.25 – 4	–	–
	Ceftaroline	0.25	0.5	0.25	0.03 – 2	–	–
	Oxacillin	4	64	1, 2	1 – >256	0	100
	Vancomycin	1	2	1	0.5 – 2	100	0
	Linezolid	1	2	1	0.25 – 16	98.1	1.9
	Daptomycin	0.25	0.5	0.25	0.12 – 1	100	–
MSS(36)	Ceftobiprole	0.12	0.25	0.25	0.06 – 0.5	–	–
	Ceftaroline	0.12	0.25	0.06, 0.12	0.03 – 0.25	–	–
	Oxacillin	0.25	0.5	0.25	0.03 – 0.5	100	0
	Vancomycin	0.5	1	1	0.25 – 2	100	0
	Linezolid	1	2	1	0.5 – 2	100	0
	Daptomycin	0.25	0.5	0.5	0.06 – 2	97.2	2.8 *
MRS(49)	Ceftobiprole	0.5	8	0.5	0.25 – 16	–	–
	Ceftaroline	0.5	4	0.5	0.12 – 8	–	–
	Oxacillin	128	>256	>256	1 – >256	0	100
	Vancomycin	1	1	1	0.25 – 2	100	0
	Linezolid	1	32	1	0.5 – >64	89.8	10.2
	Daptomycin	0.5	1	0.5	0.12 – 1	100	–
PSSP(40)	Ceftobiprole	0.016	0.06	0.016	0.004 – 0.06	100	0
	Ceftaroline	0.008	0.03	0.008	0.004 – 0.06	100	–
	Penicillin	0.016	0.06	0.016	0.004 – 0.06	100	0
	Ceftriaxone	0.016	0.06	0.016	0.004 – 0.12	100	0
	Cefepime	0.06	0.25	0.03	0.016 – 0.5	100	0
	Vancomycin	0.25	0.5	0.25	0.12 – 0.5	100	–
	Linezolid	1	1	1	0.5 – 2	100	–
	Daptomycin	0.12	0.12	0.12	0.06 – 0.5	–	–
PNSSP(70)	Ceftobiprole	0.5	1	0.5	0.06 – 1	80.0	0
	Ceftaroline	0.12	0.25	0.25	0.06 – 0.5	100	–
	Penicillin	1	2	2	0.12 – 2	0	45.7
	Ceftriaxone	0.5	2	0.5	0.25 – 2	84.3	0
	Cefepime	1	2	1	0.12 – 4	61.4	4.3
	Vancomycin	0.25	0.5	0.25	0.12 – 0.5	100	–
	Linezolid	1	1	1	0.5 – 1	100	–
	Daptomycin	0.12	0.25	0.12	0.06 – 0.25	–	–
S. pyogenes(27)	Ceftobiprole	0.008	0.008	0.008	0.004 – 0.03	100	–
	Ceftaroline	0.004	0.008	0.004	0.004 – 0.016	100	–
	Penicillin	0.008	0.008	0.008	0.004 – 0.06	100	–
	Ceftriaxone	0.016	0.03	0.016	0.008 – 0.03	100	–
	Cefepime	0.016	0.016	0.016	0.016 – 0.03	100	–
	Vancomycin	0.25	0.5	0.25	0.25 – 0.5	100	–
	Linezolid	1	1	1	0.5 – 1	100	–
	Daptomycin	0.06	0.06	0.06	0.03 – 0.06	100	–

续表 1(Continued tablet 1)

Strains(Number)	Antibiotic	MIC_{50} (mg·L^{-1})	MIC_{90} (mg·L^{-1})	MIC_{mode} (mg·L^{-1})	MIC_{range} (mg·L^{-1})	S	R
S. agalactiae(28)	Ceftobiprole	0.016	0.016	0.016	0.008 – 0.016	–	–
	Ceftaroline	0.008	0.016	0.008	0.004 – 0.016	100	–
	Penicillin	0.016	0.03	0.016	0.016 – 0.03	100	–
	Ceftriaxone	0.03	0.03	0.03	0.008 – 0.03	100	–
	Cefepime	0.03	0.06	0.03, 0.06	0.03 – 0.06	100	–
	Vancomycin	0.5	0.5	0.5	0.25 – 0.5	100	–
	Linezolid	1	1	1	0.5 – 1	100	–
	Daptomycin	0.25	0.25	0.25	0.12 – 0.25	100	–
Streptococcus spp.	Ceftobiprole	0.12	2	0.03	0.016 – 16	–	–
viridans group(25)	Ceftaroline	0.03	1	0.03	0.016 – 8	–	–
	Penicillin	0.06	32	0.03	0.016 – 128	64.0	16.0
	Ceftriaxone	0.12	16	0.12	0.03 – 64	84.0	16.0
	Cefepime	0.25	64	0.12	0.016 – 64	84.0	16.0
	Vancomycin	0.5	1	0.5	0.12 – 1	100	–
	Linezolid	1	1	1	0.5 – 1	100	–
	Daptomycin	0.25	0.5	0.25	0.12 – 1	100	–
E. faecalis(51)	Ceftobiprole	0.5	1	0.5	0.06 – 8	–	–
	Ceftaroline	4	16	2	0.5 – >32	–	–
	Ampicillin	1	2	1	0.5 – 64	98.0	2.0
	Vancomycin	1	1	1	0.5 – 2	100	0
	Linezolid	2	4	2	1 – 8	86.3	9.8
	Daptomycin	1	2	0.5	0.12 – 2	100	0

MSSA: Methicillin susceptible *Staphylococcus aureus*; MRSA: Methicillin resistant *Staphylococcus aureus*; MSSE: Methicillin susceptible *Staphylococcus epidermidis*; MRSE: Methicillin resistant *Staphylococcus epidermidis*; MSS: Methicillin susceptible *Staphylococcus* excluding *S. aureus/S. epidermidis*; MRS: Methicillin resistant *Staphylococcus* excluding *S. aureus/S. epidermidis*; PSSP: Penicillin susceptible *Streptococcus pneumoniae*; PNSSP: Penicillin non – susceptible *Streptococcus pneumoniae*; *S. pyogenes*: *Streptococcus pyogenes*; *S. agalactiae*: *Streptococcus agalactiae*; *E. faecalis*: *Enterococcus faecalis*; *: nonsusceptible; –: no breakpoints.

表 2 抗菌药物对革兰阴性菌 MIC 结果及细菌敏感、耐药率(%)

Table 2 Antibacterial activity and susceptibility (S) and resistance (R) rates (%) of antimicrobial agents against gram – negative bacteria

Strains(Number)	Antibiotic	MIC_{50} (mg·L^{-1})	MIC_{90} (mg·L^{-1})	MIC_{mode} (mg·L^{-1})	MIC_{range} (mg·L^{-1})	S	R
Non – ESBLs	Ceftobiprole	0.03	0.06	0.03	0.016 – 0.25	100	0
E. coli(50)	Ceftaroline	0.06	0.25	0.06	0.03 – 0.5	100	0
	Ceftriaxone	0.06	0.12	0.06	0.016 – 0.12	100	0
	Ceftazidime	0.12	0.5	0.12	0.06 – 1	100	0
	Cefepime	0.06	0.06	0.06	0.03 – 0.12	100	0
Non – ESBLs	Ceftobiprole	0.03	0.06	0.03	0.016 – 0.5	98.1	0
K. pneumoniae(52)	Ceftaroline	0.12	0.12	0.12	0.06 – 0.5	100	0
	Ceftriaxone	0.06	0.12	0.06	0.03 – 0.25	100	0
	Ceftazidime	0.25	0.5	0.12	0.12 – 1	100	0
	Cefepime	0.03	0.06	0.03	0.03 – 0.12	100	0
Ampicillin – susceptible	Ceftobiprole	0.06	0.06	0.06	0.016 – 0.06	100	0
H. influenzae(35)	Ceftaroline	0.008	0.016	0.008	≤0.002 – 0.06	100	–
	Ceftriaxone	0.004	0.008	0.004	≤0.002 – 0.03	100	–
	Ceftazidime	0.12	0.12	0.12	0.03 – 0.25	–	–
	Cefepime	0.12	0.12	0.12	0.03 – 0.12	100	–
	Ampicillin	0.25	0.5	0.25	0.25 – 0.5	100	0
Ampicillin – resistant	Ceftobiprole	0.5	1	0.5	0.016 – 1	48.6	10.8
H. influenzae(37)	Ceftaroline	0.12	1	0.12	0.008 – 2	83.8	16.2 *
	Ceftriaxone	0.12	0.12	0.12	≤0.002 – 0.25	100	–
	Ceftazidime	0.25	1	0.25	0.03 – 1	–	–
	Cefepime	1	2	1	0.03 – 2	100	–

续表2(Continued tablet 2)

Strains(Number)	Antibiotic	MIC_{50} ($mg \cdot L^{-1}$)	MIC_{90} ($mg \cdot L^{-1}$)	MIC_{mode} ($mg \cdot L^{-1}$)	MIC_{range} ($mg \cdot L^{-1}$)	S	R
	Ampicillin	64	>256	>256	4 - >256	0	100
M. catarrhalis(51)	Ceftobiprole	0.25	0.5	0.25	0.03 - 0.5	-	-
	Ceftaroline	0.12	0.5	0.12	0.016 - 2	-	-
	Ceftriaxone	0.5	1	0.5	0.06 - 2	98.0	0
	Ceftazidime	0.12	0.25	0.06	0.06 - 0.5	-	-
	Cefepime	1	4	1	0.5 - 4	100	0
CAZ - susceptible	Ceftobiprole	4	8	4	0.5 - 32	-	-
P. aeruginosa(104)	Ceftaroline	>32	>32	>32	8 - >32	-	-
	Ceftazidime	2	4	2	1 - 8	100	0
	Cefepime	2	8	2	0.5 - 32	98.1	1.0
CAZ - nonsusceptible	Ceftobiprole	32	256	256	2 - 256	-	-
P. aeruginosa(40)	Ceftaroline	>32	>32	>32	>32	-	-
	Ceftazidime	128	>256	128	16 - >256	0	92.5
	Cefepime	64	>256	128	8 - >256	2.5	92.5

ESBLs: Extended - spectrum β - lactamases; *K. pneumoniae*: *Klebsiella pneumoniae*; *H. influenzae*: *Haemophilus influenzae*; *M. catarrhalis*: Moraxella catarrhalis; CAZ: Ceftazidime; *P. aeruginosa*: *Pseudomonas aeruginosa*; *: Nonsusceptible; -: No breakpoints.

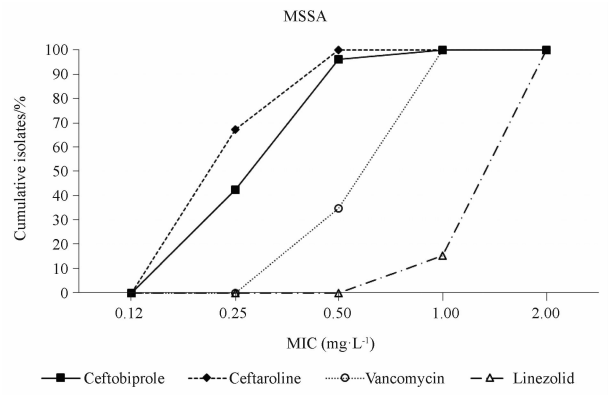

图1 头孢比罗及主要对照药对52株MSSA的累积抑菌百分比

Figure 1 Cummulative isolates (%) of ceftobiprole and main compared agents against 52 MSSA

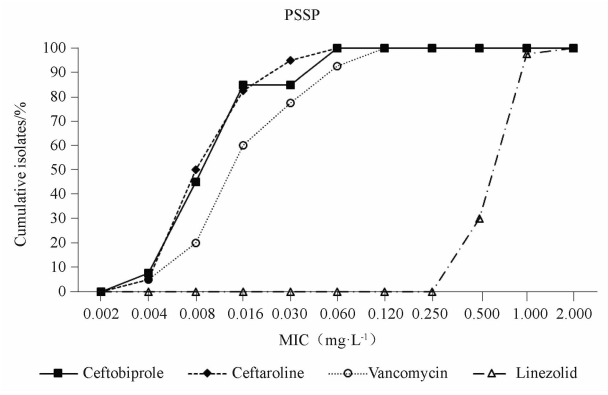

图3 头孢比罗及主要对照药对40株青霉素敏感肺炎链球菌的累积抑菌百分比

Figure 3 Cummulative isolates (%) of ceftobiprole and main compared agents against 40 PSSP (MICs of penicillin ≤0.06 $mg \cdot L^{-1}$)

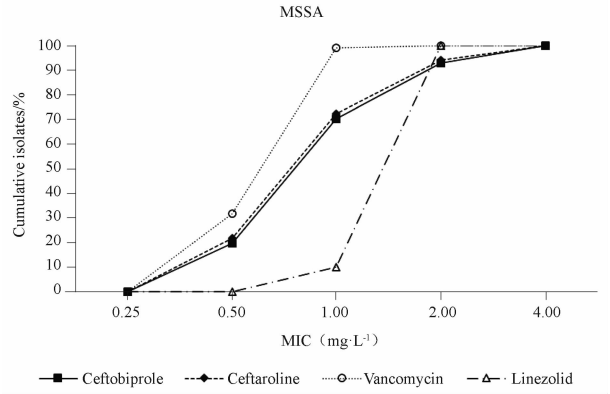

图2 头孢比罗及主要对照药对101株MRSA的累积抑菌百分比

Figure 2 Cummulative isolates (%) of ceftobiprole and main compared agents against 101 MRSA

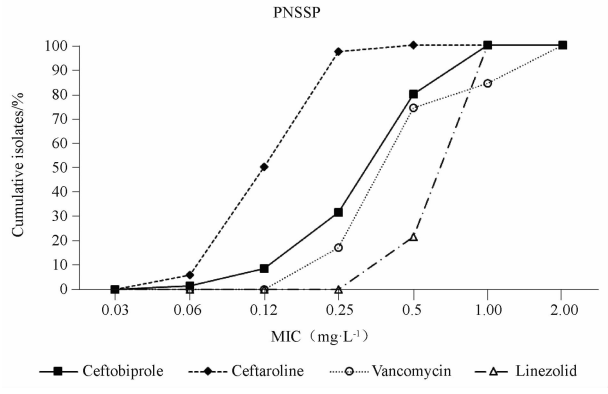

图4 头孢比罗及主要对照药对70株青霉素不敏感肺炎链球菌的累积抑菌百分比

Figure 4 Cummulative isolates (%) of ceftobiprole and main compared agents against 70 PNSSP (MICs of penicillin >0.06 $mg \cdot L^{-1}$)

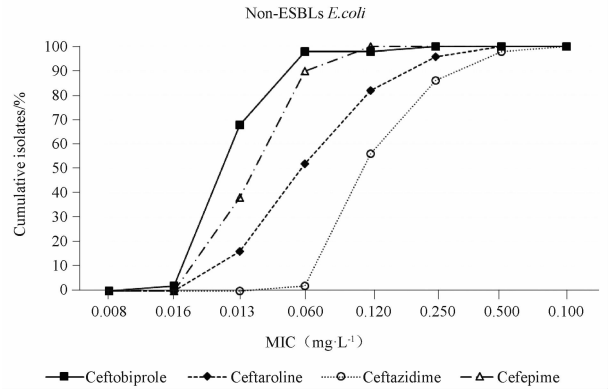

图 5 头孢比罗及主要对照药对 50 株 ESBLs 阴性大肠埃希菌的累积抑菌百分比

Figure 5 Cummulative isolates (%) of ceftobiprole and main compared agents against 50 non – ESBLs *E. coli*

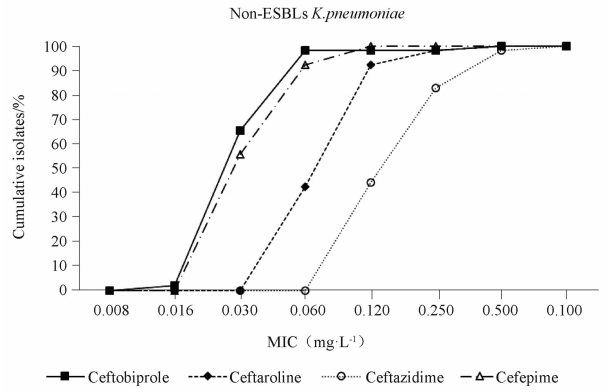

图 6 头孢比罗及主要对照药对 52 株 ESBLs 阴性肺炎克雷伯菌的累积抑菌百分比

Figure 6 Cummulative isolates (%) of ceftobiprole and main compared agents against 52 non – ESBLs *K. peumoniae*

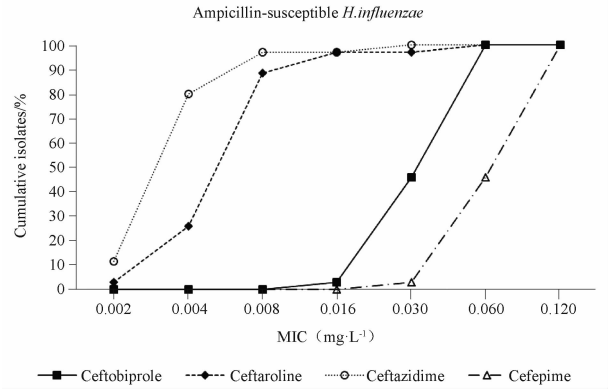

图 7 头孢比罗及主要对照药对 35 株氨苄西林敏感流感嗜血杆菌的累积抑菌百分比

Figure 7 Cummulative isolates (%) of ceftobiprole and main compared agents against 35 ampicillin – susceptible *H. influenzae*

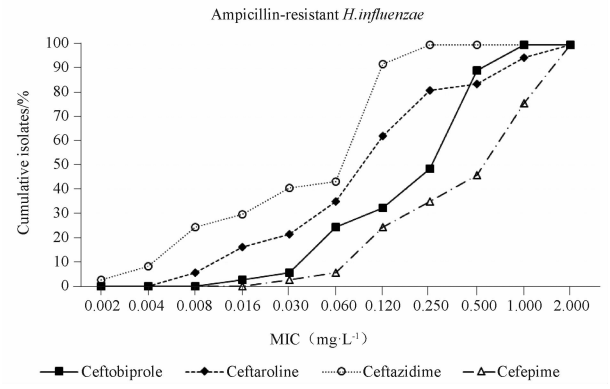

图 8 头孢比罗及主要对照药对 37 株氨苄西林耐药流感嗜血杆菌的累积抑菌百分比

Figure 8 Cummulative isolates (%) of ceftobiprole and main compared agents against 37 ampicillin – resistant *H. influenzae*

讨　论

注射用头孢比罗酯钠为深圳华润九新药业有限公司引进的第五代头孢菌素，2020 年 10 月获批药品注册证书，为国内首个第五代原研头孢菌素。适应症包括社区获得性肺炎(community – acquired pneumonia，CAP)和医院获得性肺炎(hospital – acquired pneumonia，HAP)，但呼吸机相关性肺炎除外。2024 年美国 FDA 批准头孢比罗用于金黄色葡萄球菌菌血症、急性细菌性皮肤及皮肤结构感染和社区获得性细菌性肺炎的治疗。2025 年 1 月，国家药品监督管理局药品审评中心批准头孢比罗用于 3 个月 – 18 岁儿童的 CAP 和 HAP。头孢比罗酯钠在血浆中能快速裂解形成头孢比罗发挥抗菌作用。

本研究结果显示，头孢比罗对 2019 ~ 2020 年国内临床分离葡萄球菌、链球菌属及粪肠球菌均具有较好抗菌作用，其对金黄色葡萄球菌 MIC_{50}、MIC_{90} 值及 MIC 范围与近年欧美报道[10-12]基本一致，MRSA 敏感率略低于欧美(93.1% *vs.* ≥98%)。美国的监测[12]显示 MRSA 对头孢洛林敏感率为 94.6%，明显高于本研究结果(72.3%)，提示不同国家、不同监测中菌株基因特性不同可导致监测结果有所差异。浙江大学 LI 等[13]对 2021 年 1 月至 12 月全国范围血流感染致病菌监测显示，MRSA 对头孢比罗敏感率为 99.6%，但不同基因型敏感率不同，其中 ST239 型敏感率仅 81.2%。此外，其监测中头孢比罗对甲氧西林敏感凝固酶阴性葡萄球菌 MIC_{90} 值为 1 mg · L^{-1} 略高于本研究结果(0.25 mg · L^{-1})。国家健康管理协会欧洲分会的监测项目显示，头孢比罗对青霉素中介、耐药肺

炎链球菌 MIC_{50}、MIC_{90}值分别为 0.25 mg·L^{-1}、0.5 mg·L^{-1}和 0.5 mg·L^{-1}、1 mg·L^{-1},菌株敏感率分别为97.0%和69.6%[10],此结果与本研究基本一致。美国报道[12]头孢比罗对骨关节感染患者分离粪肠球菌 MIC_{50}、MIC_{90}值分别为 0.5 mg·L^{-1}和 2 mg·L^{-1},LI 等报道头孢比罗对血流感染患者分离粪肠球菌 MIC_{50}、MIC_{90}值分别为0.25 mg·L^{-1}和2 mg·L^{-1}[13],均与本研究基本一致。

头孢比罗对 ESBLs 阴性大肠埃希菌、肺炎克雷伯菌以及氨苄西林敏感流感嗜血杆菌、卡他莫拉菌也有很好抗菌活性,菌株敏感性基本可达100%。对头孢他啶敏感铜绿假单胞菌,头孢比罗药敏结果与文献报道[10]相似。

目前有关头孢比罗耐药机制研究较少,HAWSER等[14]在对880株分离自欧洲呼吸道感染患者的MRSA药敏测试中发现3株头孢比罗不敏感菌株(MIC值均为4 mg·L^{-1}),进一步基因检测显示耐药菌株编码青霉素结合蛋白的 *mecA* 基因及其他蛋白基因存在不同突变。ZHUANG 等[15]的研究则发现,敲除头孢比罗耐药 MRSA 中替考拉宁相关 tcaA 基因后,菌株恢复对头孢比罗的敏感性。

真实世界研究及与头孢洛林对比的证据均表明,其疗效不劣于标准治疗方案,具有较高的临床治愈率。此外,头孢比罗还具有快速起效、单药或联合用药的便捷性。老年患者群体中表现出的良好耐受性与理想治愈率,使其成为治疗复杂基础疾病老年患者及难治性感染的重要选择[16]。

总之,头孢比罗对中国2019~2020年临床分离常见革兰阳性、阴性致病菌,包括甲氧西林耐药葡萄球菌、青霉素耐药肺炎链球菌等均有很好抗菌作用,与国内、欧美监测结果相似。广泛的抗菌作用与适应症及良好安全性使其成为临床抗感染治疗的重要选择之一。

参考文献:

[1] BUSH K, HEEP M, MACIELAG M J, *et al*. Anti-MRSA β-lactams in development, with a focus on ceftobiprole: The first anti-MRSA β-lactam to demonstrate clinical efficacy [J]. *Expert Opin Investig Drugs*, 2007, 16(4): 419—429.

[2] 高秀娟,权菊香,王燕龙,等. 头孢吡普抗耐甲氧西林金黄色葡萄球菌活性的研究进展[J]. 中国临床药理学杂志,2021, 28(1):64—66.

[3] SYED Y Y. Ceftobiprole medocaril: A review of its use in patients with hospital- or community-acquired pneumonia [J]. *Drugs*, 2014,74(13):1523—1542.

[4] LIVERMORE D M. Can beta-lactams be re-engineered to beat MRSA [J]. *Clin Microbiol Infect*, 2006, 12(Suppl 2): 11—16.

[5] LOVERING A L, GRETES M C, SAFADI S S, *et al*. Structural insights into the anti-methicillin-resistant *Staphylococcus aureus* (MRSA) activity of ceftobiprole [J]. *J Biol Chem*, 2012, 287(38): 32096—32102.

[6] DAVIES T A, PAGE M G, SHANG W, *et al*. Binding of ceftobiprole and comparators to the penicillin-binding proteins of *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* [J]. *Antimicrob Agents Chemother*, 2007, 51(7): 2621—2624.

[7] FDA. Ceftobiprole medocaril sodium for injection [EB/OL]. 2024-04-03 [2024-05-08]. https://www.fda.gov/drugs/development-resources/ceftobiprole-medocaril-sodium-injection.

[8] CLSI. Performance standards for antimicrobial susceptibility testing. 34th ed. CLSI supplement M100 [EB/OL]. 2024-01-27 [2024-05-08]. https://clsi.org/shop/standards/m100/.

[9] EUCAST. Breakpoint tables for interpretation of MICs and zone diameters [EB/OL]. 2024-01-01 [2024-05-08]. http://www.eucast.org/clinical_breakpoints.

[10] CANTON R, HAMED K, WIKTOROWICZ T, *et al*. *In vitro* activity of ceftobiprole and comparator antibiotics against contemporary European isolates (2016-19) [J/OL]. *JAC Antimicrob Resist*, 2022, 4(2): dlac030. 2022-03-24 [2024-05-08]. https://pubmed.ncbi.nlm.nih.gov/35350131/.

[11] HAWSER S, KOTHARI N, JEMMELY N, *et al*. Susceptibility of ceftobiprole against gram-positive and gram-negative clinical isolates from 2019 from different European territories [J]. *J Glob Antimicrob Resist*, 2022, 29: 393—397. 2022-03-10 [2024-05-08]. https://pubmed.ncbi.nlm.nih.gov/35561977/.

[12] DUNCAN L R, HAMED K A, SMART J I, *et al*. Ceftobiprole activity against gram-positive and gram-negative pathogens causing bone and joint infections in the United States from 2016 to 2020 [J]. *Diagn Microbiol Infect Dis*, 2022, 103(3): 115713.

[13] LI L, ZHOU W, CHEN Y, *et al*. *In vitro* antibacterial activity of ceftobiprole and comparator compounds against nation-wide bloodstream isolates and different sequence types of MRSA [J]. *Antibiotics* (*Basel*), 13(2): 165.

[14] HAWSER S, KOTHARI N, KARLOWSKY J A, *et al*. *In vitro* susceptibility testing of ceftobiprole against 880 European respiratory tract infection isolates of methicillin-resistant *Staphylococcus aureus* followed by whole genome sequencing of ceftobiprole-resistant isolates [J]. *Diagn Microbiol Infect Dis*, 2020, 96(4): 114978.

[15] ZHUANG H, CHEN M, HU D, *et al*. Role of tcaA, a potential target as a ceftobiprole resistance breaker in MRSA β-lactam resistance [J]. *Int J Antimicrob Agents*, 2024, 64(1): 107185.

[16] GENTILE I, GIULIANO S, CORCIONE S, *et al*. Current role of ceftobiprole in the treatment of hospital-acquired and community-acquired pneumonia: Expert opinion based on literature and real-life experiences [J]. *Expert Rev Anti Infect Ther*, 2025, 23(2-4): 217—225.

(收稿日期 2025-06-25)