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药代动力学/药效动力学在危重症患者抗生素治疗方案优化中的应用及研究进展

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摘要 危重症患者的高病死率是世界范围内重症监护医师面临的重大挑战, 有效的抗生素治疗是挽救患者生命的关键因素. 危重症患者病理生理学改变导致抗生素药代动力学(pharmacokinetics, PK)/药效动力学(pharmacodynamics, PD)发生改变, 优化抗生素给药方案是重要的应对策略. 本文对常见抗生素的PD特征、在危重症患者体内PK潜在改变, 及PK/PD在危重症患者抗生素治疗方案优化中的应用研究进展进行了综述.

关键词 危重症患者, 抗生素, 药代动力学, 药效动力学, 剂量优化

感染是危重症患者高死亡率的重要原因之一, 有效的抗生素治疗对于挽救危重症患者生命至关重要. 目前, 全球范围内不断增长的细菌耐药导致危重症患者抗生素选择面临严峻挑战, 成为医疗机构面临的现实难题. 此外, 除了前降钙素原在菌血症、肺炎等感染性疾病中对疗程判断有所帮助外, 临床仍然缺乏有助于感染诊断、程度判断等标志物检测手段. 近年来, 危重症患者机体病理生理改变导致抗生素体内药代动力学(pharmacokinetics, PK)和药效动力学(pharmacodynamics, PD)发生变化, 正常人体获得的PK/PD参数在危重症患者临床抗生素用药方案制定中的适用性受到越来越多的质疑[1]. 理想的抗生素治疗方案制定需要对药物PK/PD特征和患者的病理生理状态进行深入地整合理解, 在提高疗效的同时使药物不良反应和耐药性最小化. 因此, 了解危重症患者病理生理学的改变、抗生素的PD特征及其在危重症患者体内PK的改变对于选择合理的治疗方案和优化治疗结局具有重要意义. 本文对国内外危重症患者抗生素PK/PD相关研究进展和建议的用药方案进行综述.

1 抗生素的杀菌特征

基于PD特征, 可将抗生素分为三类: (1) 浓度依赖型: 杀菌效果与药物浓度相关; (2) 时间依赖型: 杀菌效果与药物浓度超过致病菌最低抑菌浓度(minimal inhibitory concentration, MIC)时间的长短有关, 且此类抗生素没有或仅有短的抗菌素后效应(post-antibiotic effect, PAE); (3) 时间依赖型且PAE长的药

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物: 在药物浓度低于MIC时仍能够抑制细菌生长. 各类抗生素代表药物及药效和毒性主要PK/PD指标如表1所示[2~13].

2 危重症患者体内抗生素PK特征改变

危重症患者通常伴发肝和肾功能异常、低蛋白血症、大量体液复苏、药物体内分布容积改变等情况, 以上病理生理学变化与药物理化因素共同决定了抗生素在危重症患者体内PK参数的改变.

2.1 抗生素的理化性质对危重症患者抗生素PK变化的影响

抗生素的溶解性(水溶性或脂溶性)是影响其体内分布容积和清除率的因素之一. 水溶性抗生素主要包括β-内酰胺类、氨基糖苷类、糖肽类、多黏菌素类以及利奈唑胺和氟康唑等, 这些抗生素在普通患者体内具有表观分布容积较小、主要经肾脏清除等特点. 在危重症患者体内, 水溶性药物表现为表观分布容积增大, 肾功能改变导致的清除率增加或降低. 脂溶性药物主要包括氟喹诺酮类、大环内酯类、林可霉素类, 此类药物主要经肝脏代谢清除, 在脂肪组织的广泛分布决定了其表观分布容积大, 在危重症患者体内分布容积变化较小, 而清除率受肝功能的影响而改变[14].

2.2 危重症患者病理生理改变对体内抗生素PK变化的影响

2.2.1 危重症患者体内抗生素分布容积改变

危重症患者感染发生机制复杂、机体内环境变化导致抗生素体内PK特征改变. 除药物本身理化性质外, 血浆蛋白结合是影响药物体内分布容积和体内清除率的重要因素. 约50%的危重症患者合并低白蛋白血症, 影响药物血浆蛋白结合率, 导致游离状态药物增加, 分布容积与清除率增大[15]. 此外, 体外膜肺氧合(extra-corporeal membrane oxygenation, ECMO)作为一种医疗急救技术设备, 主要用于对重症心肺功能衰竭患者提供持续的体外呼吸与循环, 尽管有研究报道ECMO可增加抗生素的表观分布容积, 目前ECMO患者的抗生素建议剂量与其他危重症患者相同[16].

2.2.2 危重症患者体内抗生素清除率改变

抗生素在体内的清除率对于制定给药方案至关重要. 肝脏是人体内介导抗生素代谢清除的重要器官. 肝功能减退时, 抗生素的选择及剂量调整需要考虑肝功能减退对该类药物体内过程的影响程度, 以及肝功能减退时该类药物及其代谢物发生毒性反应的可能性. 由于药物在肝脏代谢过程复杂, 不少药物的体内代谢过程尚未被完全阐明, 根据现有资料, 肝功能减退时抗生素临床应用分为以下4种情况: (ⅰ) 药物主要经肝脏代谢清除, 肝功能减退时体内药物浓度升高, 并

表 1 抗生素药效、毒性相关PK/PD参数

Table 1 Pharmacokinetic/pharmacodynamic ratios of antimicrobials associated with clinical efficacy and toxicity

抗生素分类	代表药物	药效			毒性			
		PK/PD比值	目标值	参考文献	毒性	阈值		参考文献
浓度依赖型	氨基糖苷类	C_{max}/MIC	>8	[2]	肾毒性	庆大霉素/妥布霉素	C_{min}>1 μg/mL	[3,4]
		AUC/MIC	>70			阿米卡星	C_{min}>5 μg/mL	
	氟喹诺酮类	C_{max}/MIC	>8	[5]	N/A	N/A	N/A	N/A
		AUC/MIC	>125		N/A	N/A	N/A	N/A
时间依赖型	青霉素类	*f*T>MIC	100% 1–4×MIC	[6,7]	神经毒性	哌拉西林	C_{min}>64~361 μg/mL	[8,9]
	N/A	N/A	N/A	N/A	肾毒性	哌拉西林	C_{min}>452 μg/mL	[8]
	头孢菌素类	*f*T>MIC	100% 1–4×MIC	[10,11]	神经毒性	头孢吡肟	C_{min}>22 μg/mL	[12]
	碳青霉烯类	T>MIC	100% 1–4×MIC	[6]	神经毒性	美罗培南	C_{min}>64 μg/mL	[8]
	N/A	N/A	N/A	N/A	肾毒性	美罗培南	C_{min}>44 μg/mL	[8]
时间依赖型且PAE长的药物	替加环素	AUC/MIC	>4.5	[13]	N/A	N/A	N/A	N/A

可导致毒性反应的发生，肝功能减退患者应避免使用此类药物，包括氯霉素、利福平、两性霉素等；(ⅱ)药物主要由肝脏清除、肝功能减退导致体内药物浓度明显升高, 但并无明显毒性反应发生, 肝功能减退患者可谨慎应用, 必要时降低剂量, 治疗过程严密监测肝功能, 包括红霉素、克林霉素、林可霉素等; (iii) 药物经肝、肾途径清除, 肝功能减退时体内药物浓度升高, 同时伴有肾功能减退患者血药浓度升高尤为明显，但无明显毒性反应发生. 严重肝病患者，尤其肝、肾功能同时减退患者在应用此类药物时需减量，包括青霉素类、头孢菌素类等; (iv) 药物主要经肾脏排泄，肝功能减退患者不需要调整剂量，包括氨基糖苷类、糖肽类抗生素等.

在急性肾损伤病理状态下，以肾清除为主要排泄途径的抗生素体内清除率会显著降低. 此外, 大约50% ICU入院患者呈高肾清除率(肌酐清除率>130 mL min^{-1} 1.73 m^{-2})状态 , 此类患者通常年龄≤50岁、男性、有外伤史, 在感染、应激等因素的作用下, 高动力型血流动力学状态发生风险明显增加，心输出量增加导致器官血流灌注量增加，肾脏滤过功能增强, 导致患者体内包括抗生素在内的药物经肾脏清除率增加[17]. 也有研究表明，合并高肾清除率危重症患者治疗失败率明显增加(27.3% *vs*. 12.9%)[18]. 另有一项针对ICU脓毒血症患者的研究发现，高肾清除率与β-内酰胺类抗生素低血药浓度相关(OR=3.3，95% CI 1.11~9.94), 标准间隔给药方式不能达到体内最佳暴露量，需要更大规模的研究来确定β-内酰胺类抗生素标准给药方案是否对高肾清除率患者的临床结果和抗生素耐药性产生负面影响[19]. 然而，临床上对急性肾损伤和高肾清除率患者的识别具有挑战性. 肾功能的评价主要基于血肌酐计算，在危重患者中，这种计算方法可高估急性肾损伤患者肾功能达80%，而低估高肾清除率患者的肾功能达42%[20,21]. 现有证据表明尿肌酐清除率可以更好地评估肾功能，用于危重症患者的抗生素剂量指导[22]. 相对于肾功能不全的患者，肾脏替代治疗增加某些抗生素(β-内酰胺类抗生素和其他小分子、低蛋白结合率和亲水性的抗生素)的体内清除，对药物清除率的影响与肾脏替代治疗装置、剂量有关. 一项Meta[23]分析表明，流速是肾脏替代治疗对体内药物清除率影响的最强预测因子，包括万古霉素(r_s=0.90; *P*=0.08)、美罗培南(r_s=0.43; *P*=0.12)、哌拉西林(r_s=0.77; *P*=0.10). 此外, 随着病情进一步恶化, 危重症患者可能出现严重的心肺功能障碍，导致器官血流灌注的减弱以及微血管循环衰竭，并最终发展为包括肝、肾在内的多器官功能障碍综合征，导致抗生素清除率降低、半衰期延长，引起抗生素体内暴露量增加, 产生毒性反应风险.

2.2.3　危重症患者体内抗生素在靶器官/靶组织浓度改变

抗生素在感染病灶靶器官或组织的浓度对于抗菌药效的发挥具有重要意义. Zhang等人[24]首次针对接受多剂量静脉注射莫西沙星的中枢神经系统分流装置相关感染患者研究发现，患者脑脊液与血清的药物AUC比值为0.7, 提示莫西沙星可能对细菌性中枢神经系统感染有治疗作用. 以往有研究报道, 抗生素在脓毒性休克患者体内的组织穿透性是健康志愿者的1/10~1/5，而在非脓毒血症患者体内抗生素组织浓度未见明显改变[25]. 因此，脓毒血症危重症患者抗生素方案的制定需要考虑靶器官或组织浓度. 目前，部分已报道的抗生素在靶部位与血清药物浓度比值如表2所示[26~45].

3　危重症患者抗生素治疗方案优化策略

危重症患者体内抗生素清除率或分布容积的改变会引起血浆药物浓度显著降低、PK/PD无法达到预期值, 从而导致抗生素治疗失败. 一项包括68家医院的多中心、观察性研究发现, 361名使用β-内酰胺类抗生素的危重症患者中，16%的患者在常规治疗中未能达到50%*f*T>MIC[46]. 另一方面，部分危重症患者脓毒血症休克后期, 由于显著的血液分流, 导致肝、肾等重要器官衰竭. 组织的低灌注影响药物体内分布, 进而引起部分抗生素体内分布容积降低. 随着脏器衰竭进展, 抗生素体内清除率进一步降低，从而引起抗生素体内蓄积, 产生潜在毒性风险. 因此, 危重症患者抗生素合理治疗方案的制定需综合考虑药物在危重症患者体内PK的改变、感染靶部位及药物的药效学特征. 目前已有研究报道多种危重症患者抗生素治疗方案的优化策略.

3.1　增加负荷剂量

及时、有效地给予抗菌素并确保早期达到治疗浓

表 2 抗生素的靶部位/血清浓度比值

Table 2 Approximate penetration into target sites relative to total antibiotic plasma exposure

	靶部位/血清浓度比值				参考文献
	肺	细胞间隙液	脑脊液		
			脑膜炎	非脑膜炎	
哌拉西林	0.39~0.63	0.2~1	0.034	0.32	[25,26]
头孢吡肟	1.04	N/A	N/A	0.103	[27,28]
头孢曲松	N/A	N/A	0.007	N/A	[29]
头孢他啶	0.21~0.42	N/A	0.057	N/A	[30,31]
美罗培南	0.20~0.29	0.31~0.39	0.047~0.25	0.39	[32]
厄他培南	0.32	0.08~0.09	N/A	N/A	[33,34]
亚胺培南	0.32~0.55	0.11~0.14	N/A	0.14	[35]
庆大霉素	0.30	0.39 ± 0.16	0.2	N/A	[36]
阿米卡星	0.09	N/A			[37]
多黏菌素	0~9.87	0.04	0.051~0.057	0.16	[38,39]
环丙沙星	0.87	0.57 ± 0.04	0.24~0.43	0.92	[40]
左氧氟沙星	1.12~1.31	0.55 ± 0.26	0.71	N/A	[41~43]
替加环素	1.32~2.41	0.63	0.11~0.85	N/A	[44,45]

度是抗感染治疗的必要条件. 在治疗初期的24小时内, 首次剂量即负荷剂量的选择依赖于药物的表观分布容积, 通常与肝、肾功能无关. 危重患者早期毛细血管渗漏和液体复苏, 细胞外容积增大, 使得表观分布容积和药物体内清除率增加, 出现稀释效应或第三间隙现象, 当使用标准抗生素剂量时, 可导致血药浓度降低. 因此, 对于危重症患者, 针对部分抗生素负荷量应高于常规标准剂量[47,48]. 最新研究表明, 与常规400 mg负荷剂量相比, 危重症患者给予800 mg负荷剂量替考拉宁可快速达到预期药物谷浓度, 获得更好的临床疗效, 且不良反应与常规负荷剂量相比未见明显增加[49]. 一项针对多黏菌素高负荷剂量治疗多药耐药鲍曼不动杆菌的疗效和安全性的前瞻性队列研究发现, 接受多黏菌素高负荷剂量的患者比常规剂量患者有更好的微生物学结果(87.9% *vs*. 70.4%; *P*=0.0006)和临床治愈的趋势, 而肾毒性不良反应在两组患者之间没有差异(52.3% *vs*. 49.4%, *P*=0.664)[50].

3.2 延长输注时间

对于时间依赖性抗菌素, 最大限度地提高*f*T>MIC是给药的目标, 特别是当疑似病原体可能具有较高MIC时(如铜绿假单胞菌), 可通过延长输注时间来实现抗生素治疗方案的优化. 大量研究表明, 延长输注时间可显著提高β-内酰胺类抗生素在呼吸机相关肺炎、脓毒血症、发热性中性粒细胞减少等危重症患者的临床疗效, 并显著降低死亡率[51~54].

3.3 治疗药物监测

治疗药物监测(therapeutic drug monitoring, TDM)是一种对生物样本中药物及相关代谢物浓度进行检测的技术. 其以PK和PD基础理论为指导, 拟定最佳的个体化给药方案, 包括药物剂量、给药时间和途径, 以提高疗效和降低不良反应, 从而达到有效而安全治疗的目的. 对于治疗窗窄、易发生不良反应且个体差异较大的抗生素, 尤其需要定期进行TDM. 20世纪90年代, 北京协和医院已开展抗生素TDM相关研究, 开启了国内相关研究的新纪元[55~57]. 1997年, 朱珠团队[57]首次报道, 头孢曲松在中国健康人PK参数与国外以往报道一致. 进一步针对院内感染患者研究表明, 头孢曲松在感染患者体内的PK特征与健康人相比未见明显差异, 且每天一次给药方案可获得良好的药效学指标和临床指标, 为该药在我国患者人群中的合理使用提供了参考, 为抗生素相关研究提供了新的思路和借鉴. 近年来, TDM用于指导抗生素在危重症患者用药相关研究

已取得进一步进展，已被证明对氨基糖苷类、伏立康唑、万古霉素有临床获益，并建议对氨基糖苷类、β-内酰胺类抗生素、利奈唑胺、替考拉宁、万古霉素和伏立康唑在危重症患者中的应用开展TDM相关工作[58].

3.4　抗菌素的联合应用

单一药物可有效治疗的感染不需联合用药，危重症患者在下列情况中有联合用药指证: (ⅰ) 病原菌尚未查明的严重感染，包括免疫缺陷患者的严重感染; (ⅱ) 单一抗生素不能控制的严重感染，两种及以上菌混合感染, 以及多重耐药菌或泛耐药菌感染; (ⅲ) 需长疗程治疗，但病原菌对某些抗生素产生耐药性的感染; 或病原菌含有不同生长特点的菌群，需不同抗菌机制的药物联合应用; (ⅳ) 毒性较大的抗菌药物，联合应用剂量可适当减少, 以降低其毒性反应.

联合用药时宜选用具有协同作用的药物联合，如青霉素类、头孢菌素类或其他β-内酰胺类与氨基糖苷类联合. 联合用药通常采用2种药物联合，3种及3种以上药物联合仅适用于个别情况，如结核病的治疗. 此外，需注意联合用药后药物相互作用及不良反应发生的风险.

4　抗生素在危重症患者中的建议用药方案

危重症患者的抗生素给药方案(图1)与抗生素PK/PD性质的改变及致病菌的敏感性密切相关，革兰阴性菌感染危重症患者抗生素经验性建议用药方案如表3所示[59~73].

4.1　β-内酰胺类

β-内酰胺类抗生素包括青霉素类、头孢菌素类和单环β-内酰胺类，此类抗生素表现为缓慢持续性杀菌特性. 此外, 碳青霉烯类抗生素的药动学性质与β-内酰胺类抗生素十分相似，且同样表现为时间依赖性药效学特征. 研究表明，维持β-内酰胺类抗生素100% *f*T>MIC可显著提高重症感染的临床治愈率(82% *vs*. 33%，P=0.002)和细菌清除率(97% *vs*. 44%，P<0.001[74]). 另有研究表明，该类药物在100% *f*T>4×MIC时对大多数革兰阴性菌具有最大的杀伤作用[47]. 然而，使用常规给药方案，危重症患者使用β-内酰胺类抗生素100% *f*T>1~4×MIC达标率仅为16%[75]. 延长输注时间或持续输注给药方案均可改善该类药物的药效学性质. 大量研究表明, 延长输注时间可显著提高β-内酰胺类抗生素的临床疗效. 近期一项纳入19项研究、1620名住院患者的Meta分析结果也表明延长输注时间可明显提高β-内酰胺类抗生素的临床疗效，显著降低死亡率[76].

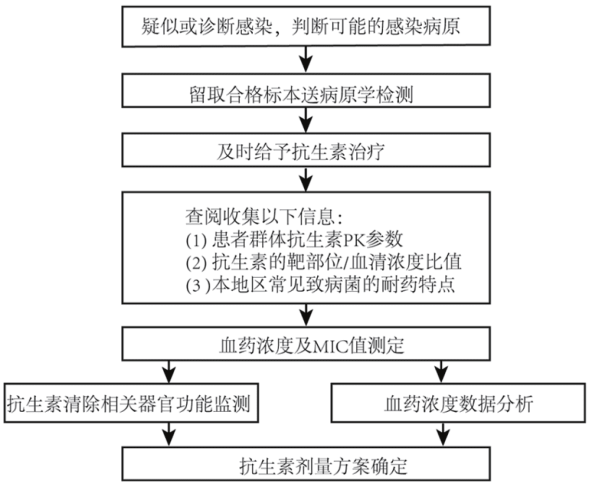

图 1　危重症感染患者抗生素用药方案制定建议流程[59]
Figure 1　Suggested process for initial administration and ongoing dosing of antibiotics for infected critically ill patients [59]

4.2　糖肽类

糖肽类由链霉菌或放线菌所产生，其结构为线性多肽. 目前临床应用的糖肽类抗菌药物有万古霉素、去甲万古霉素和替考拉宁等. Hanrahan等人[77]和Tafelski等人[78]研究表明，持续输注给药方式可显著降低万古霉素相关肾毒性，且与更早的PK/PD目标达成和较低的亚治疗浓度发生率相关. 此外，给药最初24小时内较低的药-时曲线下面积是万古霉素用于耐甲氧西林金黄色葡萄球菌菌血症治疗失败的独立危险因素, 因此建议在开始连续输注之前给予负荷剂量[79].

在一项回顾性药代动力学研究中，Matsumoto等人[80]推荐替考拉宁用于治疗危重症患者的负荷剂量用药方案为: 负荷剂量11~15 mg/kg, q12 h, 共计3次, 目标谷浓度为15~30 μg/mL. 其中，11和15 mg/kg方案在三次负荷剂量后药物谷浓度分别为17.5和27.8 μg/mL. 由于替考拉宁体内半衰期长(90~157 h), 因此建议后续

表 3 革兰阴性菌感染危重症患者抗生素经验性用药建议方案[47]a)

Table 3 Suggested empiric dosing regimens for antibiotics used for the treatment of critically ill patients with gram-negative bacterial infections [47]a)

	目前推荐剂量	危重症患者最低推荐剂量				参考文献
		CLCr >130 mL min^{-1} 1.73 m^{-2}	CLCr 60~130 mL min^{-1} 1.73 m^{-2}	CLCr 40~60 mL min^{-1} 1.73 m^{-2}	CLCr 20~40 mL min^{-1} 1.73 m^{-2}	
哌拉西林/他唑巴坦	4/0.5 g q6 h, 静脉滴注0.5 h	负荷剂量4/0.5 g, 静脉滴注0.5 h; 24/3 g 持续滴注 24 h	负荷剂量4/0.5 g, 静脉滴注0.5 h; 16/2 g 持续滴注24 h	负荷剂量4/0.5 g, 静脉滴注0.5 h; 12/1.5 g持续滴注24 h	负荷剂量4/0.5 g, 静脉滴注0.5 h; 8/1 g 持续输注24 h	[60,61]
头孢吡肟	2 g q12 h, 静脉滴注 0.5 h	负荷剂量2 g, 静脉滴注0.5 h; 8 g 持续滴注24 h	负荷剂量 2 g, 静脉滴注0.5 h; 6 g 持续滴注24 h	负荷剂量2 g, 静脉滴注0.5 h; 4 g 持续滴注24 h	LD 2 g, 静脉滴注 0.5 h; 2 g持续滴注24 h	[62,63]
头孢曲松	1~2 g q24 h	1~2 g q12 h				
美罗培南	1 g q8 h, 0.5 h 静脉滴注	负荷剂量 2 g, 静脉滴注0.5 h ; 4 g 持续滴注24 h	负荷剂量2 g, 静脉滴注0.5 h; 3 g 持续滴注 24 h	负荷剂量2 g, 静脉滴注0.5 h; 2 g持续滴注24 h	负荷剂量2 g, 静脉滴注0.5 h; 1 g持续滴注24 h	[23,64~66]
阿米卡星	15 mg/kg q24 h	30 mg/kg q; 根据TDM制定给药间隔和后续给药剂量				
多黏菌素B	0.75~1.25 mg/kg q12 h	负荷剂量 2.5 mg/kg;1.3~1.5 mg/kg q12 h (最大日剂量 250 mg)				[67]
环丙沙星	400 mg q12 h	600 mg q8 h, 48 h后 400 mg q8 h	400 mg q8 h		400 mg q12 h	[68,69]
左氧氟沙星	500 mg q24 h, 0.5-1 h 静脉滴注	1000 mg q24 h或500 mg q12 h		750 mg q24 h	750 mg q24 h	[70,71]
替加环素	负荷剂量100 mg; 50 mg q12 h	负荷剂量200 mg; 100 mg q12 h				[72,73]

a) 推荐剂量对于大多数革兰阴性菌感染患者可能达到所需的 PK/PD 目标, 其 MIC 处于临床折点

治疗中通过治疗性药物监测指导用药方案的调整. 此外, 替考拉宁血浆蛋白结合率高, 需警惕低蛋白血症对其体内游离药物浓度的影响. Roberts等人[81]研究发现, 替考拉宁在危重症患者体内的血浆蛋白结合率在71%~97%, 游离药物谷浓度为0.1~4.5 μg/mL(目标值1.5~3 μg/mL), 其血浆游离药物浓度与低白蛋白血症的严重程度呈反比.

4.3 氨基糖苷类

氨基苷类抗生素分为天然和半合成两大类. 天然来源的包括链霉素、卡那霉素、妥布霉素、庆大霉素等, 人工半合成的主要有阿米卡星、奈替米星等. 氨基糖苷类抗生素经验性的治疗方案在危重症患者中可能无法达到PK/PD目标. 一项针对阿米卡星25 mg/kg给药方案在危重症患者中的药代动力学研究发现, 25%~33%的患者未能达到PK/PD目标(C_{max}>60~64 μg/mL)[82]. 现有证据表明, 高剂量氨基糖苷类抗生素治疗, 尤其是在肾脏替代治疗患者中, 已被证实可提高PK/PD目标达成率[83]. 然而, 氨基糖苷类药物高剂量治疗的安全性是需要考量的重要问题, 有待进一步研究.

4.4 氟喹诺酮类

氟喹诺酮类主要包括环丙沙星、莫西沙星、左氧氟沙星等, 为脂溶性药物, 组织分布广泛, 在危重症患者体内表观分布容积未见明显改变. 大部分患者接受400 mg环丙沙星静脉注射, 每天三次, 可达到预期的体内暴露浓度; 少部分患者(约30%)需要600 mg, 每天三次的给药方案[68]. 而左氧氟沙星在现有研究中每日一次, 高达1000 mg的剂量下, 对于部分革兰阴性菌仍然没有达到PK/PD比值预期[70].

4.5 替加环素

替加环素对革兰阴性菌和革兰阳性菌具有广谱活性. 其为脂溶性抗生素, 可迅速渗透进入组织, 主要经

胆排泄, 仅给药量的15%以原药形式经尿清除. 目前替加环素推荐剂量对于危重患者可能是不足的, 导致接收替加环素治疗的患者死亡率明显高于其他抗生素[47]. 最新研究结果表明, 200 mg负荷剂量后每日两次100 mg替加环素用药方案更有可能达到PK/PD目标, 并显著提高危重症患者(主要是呼吸机相关肺炎)的临床治愈率[72,73].

5 总结

针对危重症患者制定抗生素用药方案时, 须了解抗生素的理化特征以及PK性质在患者体内的潜在改变, 推荐开展临床真实世界研究, 从PK/PD角度分析并结合患者临床情况进行个体化治疗, 以降低耐药性产生, 提高临床疗效, 并降低不良反应发生率.

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Application and research status of pharmacokinetics/pharmacodynamics in the optimization of antibiotic treatment regimens for critically ill patients

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Effective antibiotic treatment of critically ill patients remains a significant challenge to intensivists world-wide with persisting high mortality and morbidity rates. Pathophysiological changes in critically ill patients lead to changes in the pharmacokinetics (PK)/pharmacodynamics (PD) of antibiotics. Optimizing the current antibiotic delivery regimen is an important strategy to cope with this problem. In this paper, we review the PD characteristics and the potential changes of PK of antibiotics in critically ill patients, and the application and research progress of PK/PD in the optimization of antibiotic treatment regimens for them.

critically ill patients, antibiotics, pharmacokinetics, pharmacodynamics, dose optimization

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